Tailoring the treatment to the individual in Crohn's disease

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Edouard Louis, Jacques Belaiche and Catherine Reenaers

***Abstract*:** Crohn's disease is a heterogeneous disease with approximately 30–40% of patients having a simple benign history and the rest having a chronic progressive disease leading to complications, surgeries and potentially socio-professional marginalisation. Recent studies have shown that an early treatment with immunosuppressive treatment and/or anti-tumour necrosis factor agents could change the natural history of the disease and avoid the development of such disabling disease. The therapy should thus be tailored according to the risk of developing such disabling disease. Recent cohort studies have shown that clinical factors such as age at diagnosis, disease extent, disease location and behaviour at diagnosis were predictive for the development of severe or disabling disease and could be used in helping the physician to tailor therapy.

***Keywords*:** Crohn's disease, tumour necrosis disease, tailored therapy

Introduction

Crohn's disease (CD) is a chronic immune mediated inflammatory disorder affecting the gastrointestinal tract. CD is due to an abnormal innate and adaptive immune response to the intraluminal intestinal material, mainly microbial [Xavier and Podolsky, 2007]. Although there is no definitive curative treatment, mesalazine may have some efficacy in superficial mucosal CD lesions, steroids are very effective to induce clinical remission of moderate-to-severe CD but have a low power to heal mucosa and are associated with important toxicity contraindicating prolonged treatments, immunosuppressive drugs (essentially purine analogues and methotrexate) and above all anti-tumour necrosis factor (TNF) agents can induce and maintain remission with a high proportion of mucosal healing, leading to a decreased need for surgeries and hospitalisations [Feagan *et al.* 2008; Vernier-Massouille *et al.* 2008; Lichtenstein *et al.* 2005]. Immunosuppressive drugs and anti-TNF agents are associated with a slight increase in the risk of lymphomas and opportunistic infections [Toruner *et al.* 2008; Siegel *et al.* 2008; Kandiel *et al.* 2005]. While all clinicians dealing with inflammatory bowel disease (IBD) have in mind these characteristics of available drugs, it remains difficult to choose the right treatment for a given patient at a given timepoint. The choice of treatment must be integrated in a long-term therapeutic strategy aimed at normalising the quality of life and everyday life of the patients. The tailoring of treatment is precisely this adaptation of the treatment to an individual patient. It may be based on simple clinical characteristics such as disease location, disease behaviour (profile of complications), the age of the patient, past medical treatments or surgeries or severity of the flare. In the near future, we may also be helped by genetic, pharmacogenetic or serological markers. But for the time being, one topic that has emerged over the last 2–3 years is the tailoring of the treatment based on risk factors for developing severe disease. The idea behind this concept is that if one wants to change the natural history of CD with its burden, one has to intervene effectively before the development of all these complications. Therefore, the points to discuss are the following:

- What is the natural history of CD?
- What is a severe disease and what are the complications one wants to avoid?
- What are the predictors for such severe disease?
- What therapeutic strategy should be proposed?

Correspondence to:
Edouard Louis, MD, PhD
Department of Gastroenterology, CHU of Liège and GIGA Research, University of Liège, Belgium
edouard.louis@ulg.ac.be

Jacques Belaiche
Catherine Reenaers
Department of Gastroenterology, CHU of Liège and GIGA Research, University of Liège, Belgium

Natural history of Crohn's disease

In the majority of patients, CD presents as an uncomplicated disease. About 80% of them have purely inflammatory lesions without stricture or perforating complication [Cosnes *et al.* 2002; Louis *et al.* 2001]. These stricturing and perforating complications will develop over time and after 10 years, roughly one-third of patients develop stricturing disease and another third perforating disease [Cosnes *et al.* 2002; Louis *et al.* 2001]. The prevalence of perianal complications also increases with disease duration, from 12% one year after diagnosis to 26% after 20 years [Hellers *et al.* 1980]. These complications lead to surgical resections, and after 20 years, up to 80% of patients have to undergo surgery [Mekhjian *et al.* 1979]. CD complications that require hospitalisations and surgeries have been qualified as disabling disease. In a landmark study, the Saint-Antoine team in Paris tried to quantify such disabling disease, defined by disease complications, surgeries, hospitalisations, chronic active symptoms and requirement for steroids, immunosuppressive treatments or biologicals, and developing within 5 years after diagnosis [Beaugerie *et al.* 2006]. In their tertiary referral centre, more than 80% of patients had developed such disabling disease within 5 years after diagnosis. In two further confirmatory works coming from a population-based study in Minnesota and from a general hospital in Belgium, the percentages of disabling disease within 5 years after diagnosis were between 50% and 60% [Loly *et al.* 2008; Seksik *et al.* 2007]. These numbers are more in agreement with other population-based studies from Europe and Scandinavia, showing absence of surgery or even relapse within 5–10 years after the first flare in up to 40% of patients [Wolters *et al.* 2006; Munkholm *et al.* 1995].

Unemployment may also be a consequence of complicated or disabling CD. Both European and North American studies have shown both an increased risk of unemployment [Feagan *et al.* 2005; Longobardi *et al.* 2003] and earlier grant for disability allowances in CD as compared to controls or other diseases [Sonnenberg, 1989].

What is severe Crohn's disease?

Many different definitions have been used to define severe CD. This emphasises the variable thresholds that patients and physicians may have to define a severe disease. In the Saint-Antoine study, the term of disabling disease encompassed a broad number of situations from simply chronic active debilitating symptoms or even more than two courses of steroids, to definitive stoma or extensive small bowel resection [Beaugerie *et al.* 2006]. This definition may be considered by some as too broad and the authors of the present review tried in a following study to adopt a more stringent definition [Loly *et al.* 2008]. We defined a severe disease by the development of severe nonreversible tissue damage often leading to surgeries. Our definition included at least two small bowel resections or a unique resection of more than 50 cm of small bowel, any colonic resection, a definitive stoma or the development of complex perianal disease. Obviously the limits to define severe CD are partly subjective. One could propose that a disease is qualified as severe when it interferes for a significant period of time with normal socio-professional and/or familial activities, when it has a negative impact on the important orientations a patient has to take during their life or when it impacts significantly and durably on the general health of the patient. It thus depends on the patient's lifestyle, age, profession and expectations. Beyond that, the definition of severe CD only makes sense if a specific therapeutic strategy is proposed accordingly. Here, there will also be an interaction between the benefit/risk or even the cost/benefit ratio of drugs or therapeutic strategies and the threshold for the definition of severe CD. If one considers a treatment which is both very effective, cheap, safe and well tolerated, it is clear that the threshold for the definition of severe CD will be very low and that the vast majority of the patients would be treated with this drug. If one now considers, a mildly effective drug that is quite expensive, not very well tolerated and with important safety issues, it is evident that the threshold for severe disease will be much higher and that this drug will be prescribed in a minority of patients. We could thus propose to represent the definition of poor-prognosis CD with a triangle integrating all these elements (Figure 1), the shape of which would vary according to the clinical setting, leading to different types of definitions of severe CD each including a variable proportion of the CD population.

Predictive factors for the development of severe CD

A substantial number of recent studies have aimed at disclosing predictive factors for the development of severe CD (Table 1). Those factors or models of prediction are of course directly

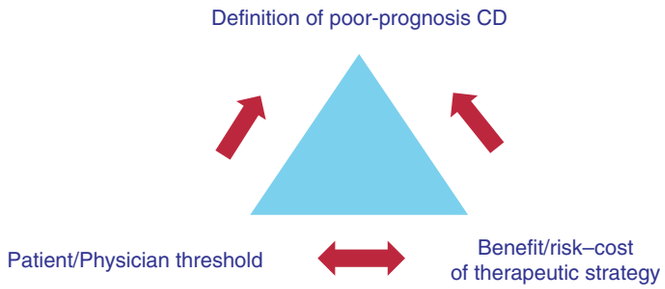

Figure 1. The poor-prognosis triangle for Crohn's disease (CD). There is no unique definition of poor-prognosis CD. It depends on the patient's (and physician's) threshold for considering severe or disabling CD. This relates to patient's expectations and socio-professional situation. The patient's threshold will also be influenced by the benefit/risk ratio of the therapeutic strategy that is proposed accordingly. These interacting factors will determine what is considered as a severe or disabling CD on an individual basis and therefore the predictive factors that may be used to tailor therapy on an individual basis.

Table 1. Independent predictors of poor-prognosis Crohn's disease.

Outcome	Predictors	Validated	Reference
Stricturing and/or penetrating disease, surgical resection	Ileal location	Yes	Louis *et al.* [2003]; Ahmad *et al.* [2002]; Henckaerts [2008]
	Smoking	Yes	Louis *et al.* [2003]; Brant *et al.* [2003]
	Antibacterial and anti-mannan antibodies	Yes	Dubinsky *et al.* [2008]; Rieder *et al.* [2008]
	Genetic markers	No	Henckaerts [2008]
Perianal disease	Disease location	Yes	Hellers *et al.* [1980]; Henckaerts [2008]
	Smoking	Yes	Henckaerts [2008]; Louis *et al.* [2003]
Colectomy	Deep colonic ulcers	No	Allez *et al.* [2002]
Disabling disease	Age at diagnosis, steroids for the first flare, ileo-colonic disease, perianal lesion	Yes	Beaugerie *et al.* [2006]; Loly *et al.* [2008]; Seksik *et al.* [2007]
Nonreversible tissue damage	Significant weight loss at diagnosis, stricturing behaviour at diagnosis	No	Loly *et al.* [2008]

linked to the definition of severe CD that was chosen by the investigators. The development of stricturing or penetrating behaviour is mainly associated with ileal location of the disease [Louis *et al.* 2003]. Another factor that may favour such evolution and the requirement of early surgery is active smoking [Brant *et al.* 2003]. Anti-*Saccharomyces* antibodies and CARD15 variants have also been associated with such behaviours but the results of large multivariate analyses indicate that these associations are secondary to a true association with ileal location [Ahmad *et al.* 2002]. Other antibacterial or mannan antibodies may also predict the development of stricturing and penetrating behaviour. The concentration and the number of positive antibodies have been significantly associated with the time to development of these complications in several European and North American cohorts [Dubinsky *et al.* 2008; Rieder *et al.* 2008]. Perianal disease has been consistently associated with disease location, affecting 12% of patients with ileal disease, 41% of patients with colonic disease, and almost all patients with rectal disease (92%) [Hellers *et al.* 1980]. In a recent study, the Leuven team aimed at modelling the prediction for the development of stricturing disease, internal penetrating disease, perianal disease or the requirement for surgery, integrating a large number of genes recently described as associated with CD, serological markers, clinical characteristics, and environmental factors such as smoking [Henckaerts, 2008]. Although the results of this study are still preliminary and have no clinical impact, this work shows the direction one has to follow for further improving prediction in CD.

A colectomy is probably to be considered as a severe complication of CD. In an interesting pilot study, it was shown that the presence of deep ulcers covering at least 10% of one colonic segment was associated with a high risk of colectomy (up to 60%) over a relatively short period of time of 3 years [Allez *et al.* 2002].

The Saint-Antoine team in Paris has worked on a more complex definition of disabling disease within 5 years after the diagnosis (see above). After multivariate analysis, an age below 40 years, a treatment of the first flare of CD with steroids and the presence of perianal lesions were independently associated with such disabling disease [Beaugerie *et al.* 2006]. These factors were at least partly confirmed in two independent cohorts [Loly *et al.* 2008; Seksik *et al*. 2007]. In the Belgian cohort however the multivariate analysis selected ileocolonic location beside age at diagnosis and need for steroids to treat the first flare of CD [Loly *et al.* 2008]. Notably, ileocolonic location was also a predictive factor in the Saint-Antoine cohort in univariate analysis. As mentioned earlier, another study is aimed at defining predictors for the development of nonreversible gastrointestinal lesions [Loly *et al.* 2008]. The development of such lesion was associated in multivariate analysis with both a significant weight loss and stricturing behaviour at diagnosis.

Overall, a young age at onset and a complicated, deeply ulcerating or extensive disease at diagnosis may be considered as predictive of poor outcome. Although not extensive, some particular locations may be considered by themselves as problematic because they are associated with a high risk of definitive disabling symptoms and/or disabling surgeries, particularly if they are associated with deep ulcers and transmural lesions: these are rectal and duodenal locations.

Tailored therapeutic strategies

Bearing in mind the natural history of CD, and particularly the fact that approximately 40% of patients will have benign nonevolutive disease while 60% will develop complicated or disabling disease, there are probably two types of mistakes in CD management as follows:

- undertreat patients who develop disabling or complicated CD
- overtreat patients who would anyway have a benign disease course.

There are also globally two main therapeutic strategies one can propose to patients – bottom-up and top-down strategies. In the bottom-up strategy, mesalazine, steroids, immunosuppressive drugs and anti-TNF treatments are given successively depending on the response of the patient to previous treatments. Globally, this strategy is the one that has been used in routine practice for decades now and has proven to be unable to change the natural history of CD, particularly to avoid disease complications and surgeries [Cosnes *et al.* 2005]. This is particularly true when this strategy is applied with a low proactivity of the physician and a relative slowness to prescribe immunosuppressive drugs and/or anti-TNF therapy. Indeed, in routine practice, even in a tertiary referral centre and despite a progressive increase in the use of immunosuppressive treatment over the last two decades, most recently only 30% of patients were treated with immunosuppressive treatment over the first year of disease [Cosnes *et al.* 2005].

In comparison, it is striking to note that in the so-called 'step-up versus top-down' study, around 70% of patients were under immunosuppressive drug one year after inclusion in the bottom-up group [D'Haens *et al.* 2008], suggesting a much more proactive approach of the physician in such study protocol than in routine practice. This could be called an optimised bottom-up strategy and long-term results of such strategy on hospitalisations and surgeries will be very interesting to know. The relative slowness to start an immunosuppressive treatment in CD patients in routine practice may also be related to the hesitance of patients to start therapies with potential serious side effects and adverse events. In opposition to the classical bottom-up strategy, the early use of immunosuppressive treatment in the paediatric population [Vernier-Massouille *et al.* 2008] and the use of anti-TNF treatments [Feagan *et al.* 2008; Lichtenstein *et al*. 2005] have recently been associated with a decreased need for surgeries and hospitalisations, indicating an impact on natural history and not only on disease symptoms control. According to these considerations, it would be logical to propose the early use of immunosuppressive treatment and/or anti-TNF in patients presenting with risk factors for poor prognosis disease, particularly when, for socio-professional reasons, the patient's expectations are high. For other patients, a bottom-up approach may still be applied. However, as the currently available predictive factors are far from

having a 100% negative predictive value, one should encourage physicians to use an optimised bottom-up approach, avoiding waiting too long before upgrading the treatment when the disease is progressing.

Conclusion

Predictive factors for the development of poor-prognosis CD have been established over the last few years. These factors, together with patients' expectations, must now be taken into account when deciding treatment strategies. Rather than applying uniform bottom-up or top-down strategies in CD, the treatment should be tailored to the individual to optimise benefit/risk ratio.

Conflict of interest statement

None declared.

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