Journal of Crohn's and Colitis (2013) 7, 820–826

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SPECIAL ARTICLE

When do we dare to stop biological or immunomodulatory therapy for Crohn's disease? Results of a multidisciplinary European expert panel ☆

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Received 5 April 2013; accepted 15 April 2013

KEYWORDS
Crohn's disease;
Azathioprine;
Anti-TNF drugs;
Treatment cessation;
Treatment stopping rules

Abstract

Background: Safety and economic issues have increasingly raised concerns about the long term use of immunomodulators or biologics as maintenance therapies for Crohn's disease (CD). Despite emerging evidence suggesting that stopping therapy might be an option for low risk patients, criteria identifying target groups for this strategy are missing, and there is a lack of recommendations regarding this question.

Methods: Multidisciplinary European expert panel (EPACT-II Update) rated the appropriateness of stopping therapy in CD patients in remission. We used the RAND/UCLA Appropriateness Method, and included the following variables: presence of clinical and/or endoscopic remission, CRP level, fecal calprotectin level, prior surgery for CD, and duration of remission (1, 2 or 4 years).

☆ Conference presentation: this work was selected as one of the best abstracts at ECCO Congress in Vienna, on February 14–16, 2013, and results were presented orally in a session of the main scientific program.

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[1] See Appendix A.

1873-9946/$ - see front matter
http://dx.doi.org/10.1016/j.crohns.2013.04.013

Results: Before considering withdrawing therapy, the prerequisites of a C-reactive protein (CRP) and fecal calprotectin measurement were rated as "appropriate" by the panellists, whereas a radiological evaluation was considered as being of "uncertain" appropriateness. Ileo-colonoscopy was considered appropriate 1 year after surgery or after 4 years in the absence of prior surgery. Stopping azathioprine, 6-mercaptopurine or methotrexate mono-therapy was judged appropriate after 4 years of clinical remission. Withdrawing anti-TNF mono-therapy was judged appropriate after 2 years in case of clinical and endoscopic remission, and after 4 years of clinical remission. In case of combined therapy, anti-TNF withdrawal, while continuing the immunomodulator, was considered appropriate after two years of clinical remission.
Conclusion: A multidisciplinary European expert panel proposed for the first time treatment stopping rules for patients in clinical and/or endoscopic remission, with normal CRP and fecal calprotectin levels.

Contents

1. Introduction

The important question of when and whether to stop treatment in Crohn's disease (CD) has so far received only limited attention in clinical trials, in contrast to the topics of induction of remission and of maintenance therapy. The decision as to whether a specific maintenance treatment should be continued is guided, as is the case in all therapeutic decisions, by balancing expected benefits against potential risks.

Biological and immunosuppressive therapies represent a significant progress in the treatment of Crohn's disease and have profoundly influenced clinical practice. The benefits of azathioprine, 6-mercaptopurine[1,2] and methotrexate[3] as well as anti TNF[4–11] on the prevention of relapses have been demonstrated in several randomized controlled trials. In a multicenter, randomized, enhance double blind, non-inferiority withdrawal trial on 40 (vs. 43) CD patients in remission induced by azathioprine for over 3.5 years, the mean relapse rate after 1.5 years of follow-up was three times higher in patients who stopped azathioprine compared to those continuing the drug.[12] In an extension study of 66 patients who stopped azathioprine, 63% did, however, suffer a relapse within 5 years, as did 39% of the subgroup of patients presenting no known risk factors (CRP level < 20 mg/l or neutrophil count $< 4.0 \cdot 10^9$/l or haemoglobin level > 12 g/dl)[13]; retreatment with azathioprine in the event of relapse was, however, successful in 80% of patients. On the other hand, Louis et al. showed that, in a prospective study of 115 CD patients in remission without steroids for at least 6 months, treated for more than a year with a combined therapy of infliximab and an immunomodulator,[14] infliximab withdrawal had an overall 1-year relapse rate of 44%, but only 15% for those patients who present no more than two risk factors (male gender, absence of surgical resection, leukocyte count > 6 G/L, fecal calprotectin >300 μg/g). Retreatment was also effective in 88% of patients who suffered a relapse. In addition, safety issues such as infections and neoplasia in the context of long-term immunomodulatory and anti-TNF, mostly in the case of combination therapy,[4] are still of significant concern to both patients and physicians. Hence, higher risks of lymphoproliferative disorders[15–17] and non-melanoma skin cancer[18] have been documented in patients receiving long-term immunosuppressive drugs.[19] Furthermore, the significant cost of anti-TNF treatment is of increasing concern in the current climate of budget constraints in healthcare systems.

Thus, establishing clear recommendations on how to identify patients eligible for a "drug holiday" is urgently needed. A multidisciplinary European expert panel (EPACT-II) convened in 2007 to develop explicit appropriateness criteria[20–23] regarding CD treatment. During an update meeting in October 2012, the panel evaluated when and under which conditions it was appropriate to consider withdrawal of CD treatment.

2. Materials and methods

2.1. Use of the RAND/UCLA appropriateness method

An appropriate medical procedure is defined as one in which the expected health benefits exceed the expected negative consequences, exclusive of any cost considerations.[24] We used the RAND/UCLA appropriateness method to assess appropriateness of stopping CD treatment. This method has previously been used to develop criteria for the appropriateness of many and sundry healthcare treatments, often when in situations where clear-cut evidence obtained through well-conducted clinical trials or high-quality observational studies is lacking. The method "is arguably the most respected approach to defining appropriate care".[25] The method comprised five steps[1]: a comprehensive literature review,[2] the selection of a multidisciplinary panel expert,[3] the identification of main clinical situations, each comprising a set of scenarios corresponding to typical patients,[4] a first individual rating round,[5] and a panel meeting with a second re-rating round of all scenarios.

The first European Panel on the Appropriateness of Treatment of Crohn's disease (EPACT-I) convened in 2004, followed by an update in 2007 (EPACT-II).[20–23] In October 2012 an EPACT-II Update Panel, formally endorsed by the European Crohn & Colitis Organisation ECCO, convened to examine scenarios for which evidence had changed since 2007. In addition, the timely issue of when to withdraw long-term therapy with immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) and/or anti-TNF drugs was assessed. Relevant articles published between 2007 and 2012 were retrieved, to complement and update the review previously performed for the 2007 EPACT-II Panel. Clinical scenarios reflecting real practice were formulated in 2007 and modified for the EPACT-II Update Panel as necessary, taking into account current evidence. For each of these scenarios, experts rated the level of appropriateness on a 9-point scale (1 = extremely inappropriate, 5 = uncertain, 9 = extremely appropriate), based on the available published evidence and their own expertise.

Appropriateness was calculated using the median of ratings and categorized as inappropriate (median 1 to 3), uncertain (median 4 to 6) and appropriate (median 7 to 9). The disagreement between panellists was calculated using the IPRAS method,[26] defined as IPRAS = 2.35 + (AI * 1.5), where AI is an index of asymmetry defined by AI = abs(5 − (p70 + p30)/2). This index was defined to provide a disagreement assessment as close as possible to the classic definition of ≥ 3 ratings in each extreme (1-3 and 7-9) for a panel of 9 panellists. An indication was rated with disagreement when the inter-percentile range (IPR) between percentiles p30 and p70 was larger than IPRAS. In the case of disagreement between panellists, the indication was considered of uncertain appropriateness.

2.2. Variables and definitions

The parameters considered for the assessment of the decision to withdraw therapy were as follows: presence of clinical and/or endoscopic remission, evaluated by colonoscopy, imaging techniques (preferentially MRI or US, but other methods may also apply),[27] CRP and fecal calprotectin level measurements[28]; length of remission under treatment (1, 2 or 4 years); and prior surgery for CD. Prior to considering therapy withdrawal at 1, 2 or 4 years, the panellists evaluated the appropriateness of assessing the following parameters to aid in the decision to stop CD therapy: imaging, CRP level, fecal calprotectin level, and endoscopic evaluation.

Stopping rules were assessed for patients with immunomodulatory treatments (azathioprine, 6-mercaptopurine, methotrexate) or anti-TNF drugs (infliximab, adalimumab, certolizumab pegol) or combined therapy (combined use of one immunomodulator and of one anti-TNF drug). For combined therapy the panellists evaluated the appropriateness of withdrawing the anti-TNF drug while continuing the immunomodulator.

The panellist agreed on the following definitions: clinical remission was defined as Crohn's Disease Activity Index CDAI < 150); endoscopic remission was defined as absence of endoscopic lesions (erosions and/or ulcers) at ileo-colonoscopy; deep remission was defined as clinical and endoscopic remission as well as biochemical remission (CRP < 5 mg/l, fecal calprotectin < 50 μg/g).

3. Results

3.1. Epact-II-Update Panel

Ten European experts – eight gastroenterologists and two surgeons (listed in Appendix A) – convened in Zurich on the 5th of October 2012 for a one-day meeting. They rated a total of 1030 clinical scenarios, of which 216 focused on modalities used to assess remission and treatment withdrawal (Table 1).

3.2. Tools to monitor disease activity

CRP and fecal calprotectin level measurements were judged to represent appropriate surrogate markers to monitor clinical and/or endoscopic remission in luminal ileocolonic CD patients with or without prior CD-related surgery (Tables 2 and 3). Imaging techniques were considered appropriate in patients with prior CD-related surgery, and who were in clinical remission under combination therapy alone (anti-TNF +

Table 1 Main clinical CD presentations.

Main clinical presentation	Number of clinical scenarios
Mild- to low-moderate active luminal CD	96
High-moderate to severe CD	48
Steroid-dependent & refractory CD	42
Fistulizing CD	45
Maintenance of medically-induced remission of CD	495
Maintenance of surgically-induced remission of CD	72
Extra-intestinal manifestation of CD	16
Monitoring modalities for luminal ileo-colonic CD in remission	168
Stopping rules for patients in remission	48

Table 2 Appropriateness of monitoring modalities for luminal ileocolonic CD in clinical remission with (A) or without (B) prior CD related surgery. Color code: yellow = uncertain, green = appropriate.

(A)	Time of assessment		
Modalities	Year 1	Year 2	Year 4
Ileo-colonoscopy	(a, c) (b)		
Imaging techniques		(a, b) (c)	(a, b) (c)
CRP			
Calprotectin			

(B)	Time of assessment		
Modalities	Year 1	Year 2	Year 4
Ileo-colonoscopy			
Imaging techniques			
CRP			
Calprotectin			

Patients treated with (a): azathioprine/6MP, methotrexate, (b): anti-TNF only, (c): anti-TNF + immunomodulator.

immunomodulator). For a patient in clinical and endoscopic remission, or in clinical remission only without any previous CD-related surgery, imaging techniques were judged as uncertain monitoring tools. Performing an ileo-colonoscopy was considered appropriate at year 1, but only for patients with anti-TNF therapy, with or with an immunomodulator or without previous CD-related surgery. At year 4, ileo-colonoscopy was considered appropriate to monitor endoscopic remission, irrespective of the type of maintenance therapy and the prior history of CD-related surgery.

3.3. Treatment withdrawal

The panel judged it "appropriate" to stop maintenance treatment of azathioprine/6MP, methotrexate, or an anti-TNF drug, with or without an immunomodulator, after 4 years for luminal ileocolonic CD patients in clinical remission who had prior CD related surgery (Table 4) or who were in clinical and endoscopic remission (Table 5). The time grid proposed was 1, 2 and 4 years of disease course. It was assumed that patients were taking maintenance therapy resulting in clinical or clinical and endoscopic remission for the entire period of the time grid. The withdrawal of anti-TNF therapy was considered appropriate after 4 years for patients in clinical remission only, and after 2 years for patients in clinical and endoscopic remission. For patients under combined maintenance therapy, stopping the anti-TNF drug was judged appropriate after 2 years of clinical and/or endoscopic remission.

Table 3 Appropriateness of monitoring modalities for luminal ileocolonic CD in clinical and endoscopic remission for a patient with or without prior CD related surgery, treated with azathioprine/6MP, methotrexate, anti-TNF +/− immunomodulator. Color code: yellow = uncertain, green = appropriate.

	Time of assessment		
Modalities	Year 1	Year 2	Year 4
Imaging techniques			
CRP			
Calprotectin			

4. Discussion

This article reports how international IBD experts, the EPACT-II Update panel, recommended monitoring Crohn's patients under maintenance therapy with immunomodulators and/or anti-TNF drugs, and at which time points they would consider it appropriate to stop these treatments while basing their decisions on biological and endoscopic monitoring parameters. The decisions include the use of monitoring tools themselves defined by appropriateness scenarios. For patients in clinical and endoscopic remission or with prior CD-related surgery, the panel judged appropriate to stop a biological or immunosuppressive maintenance treatment after 4 years. The panel also considered appropriate to stop biological therapy, being given alone or in combination therapy, after 2 years for patients in clinical and endoscopic remission.

While most of the scientific efforts have been spent in studies assessing the potential of different drugs to induce and maintain remission in Crohn's disease, stopping rules of biological and immunosuppressive therapy have not

Table 4 Appropriateness of treatment withdrawal for luminal ileocolonic CD in clinical remission only for a patient with (A) or without (B) prior CD related surgery. Color code: red = inappropriate, yellow = uncertain, green = appropriate.

(A)	Time of assessment		
Treatment	Year 1	Year 2	Year 4
Azathioprine/6MP			
Methotrexate			
Anti-TNF			
Anti-TNF + immunomodulator			

(B)	Time of assessment		
Treatment	Year 1	Year 2	Year 4
Azathioprine/6MP			
Methotrexate			
Anti-TNF			
Anti-TNF + immunomodulator			

Table 5 Appropriateness of treatment withdrawal for luminal ileocolonic CD in clinical and endoscopic remission for a patient with or without prior CD related surgery. Color code: red = inappropriate, yellow = uncertain, green = appropriate.

	Time of assessment		
Treatment	Year 1	Year 2	Year 4
Azathioprine/6MP			
Methotrexate			
Anti-TNF			
Anti-TNF + immunomodulator			

previously been conceptualized. Expected benefits and risks of treatment, according to the best published evidence, should however drive the decision to dare stopping such treatments. Moreover, all healthcare systems are currently facing major budget constraints. Policymakers may become critical regarding the appropriateness of indication and overall duration of costly treatments. When to stop such treatment is thus of similar importance as when to start it, in particular for a chronic, destructive, progressive and potentially disabling, life-long condition like Crohn's disease. For instance, the risk of developing lymphoma and non-melanoma cutaneous tumors is increasing over time under azathioprine treatment.[15–18] Trials investigating the consequences of immunosuppressive or biological therapy withdrawal[12,14,29] have defined the background relapse risk and related factors. The time limit of four years suggested to the panellists' assessment was set in analogy to studies evaluating the outcome after withdrawal of azathioprine. There are no established guidelines regarding the duration for biological treatments in inflammatory bowel diseases and scant evidence exists to guide the clinician in making the decision to stop treatment. It has been shown that clinical relapse occurs frequently when biological or immunosuppressive therapy is stopped.[30] Relapse predictive factors have been identified in an azathioprine withdrawal trial[12]: CRP levels > 20, steroid-free disease course < 50 months, and hemoglobin levels < 12 g/dl. In patients receiving combined treatment with azathioprine and infliximab, withdrawal of infliximab resulted in a 50% relapse rate within one year.[14] Risk factors for relapse included male sex, absence of prior surgery, leukocytes count $>6 \times 10^9$/l, hemoglobin levels <145 g/l, CRP levels >5.0 mg/l, and fecal calprotectin levels >300 μg/g. In the study of Louis et al., patients presenting no more than two risk factors had a much lower relapse rate (15%).

Patients may benefit from treatment discontinuation when remission is envisioned beyond the control of clinical symptoms. In contrast to conditions such as rheumatoid arthritis, this new concept is just emerging in inflammatory bowel disease, implying a state of remission with little or no risk of progression.[31] Ultimately, deep remission might impact on the disability of the patients and their need for surgery.[32] There is no widely accepted definition of deep remission. Most clinicians would accept that these patients experience both an excellent control of clinical symptoms coupled with endoscopic remission (mucosal healing, i.e., absence of any endoscopic lesions).[32–37] The definition of deep remission is of particular importance in CD, as the correlation between clinical symptoms and endoscopic activity is weak: endoscopic assessment is therefore mandatory. It has to be acknowledged that the EPACT-II Update Panel did not focus on fine-tuning the definition of deep remission as such. We did not, for example, focus on whether minor endoscopic lesions, histological inflammatory abnormalities or supra-normal values of calprotectin in an asymptomatic patient would still be considered as deep remission.

Monitoring of biological parameters (CRP, calprotectin) was unanimously recommended after 1, 2 and 4 years if therapy withdrawal were to be considered. Colonoscopy was uniformly proposed at 4 years. Surprisingly, colonoscopy was deemed appropriate after 1 year of treatment but uncertain at 2 years, which probably reflects the current practice of assessing mucosal healing at 1 year in patients treated with immunosuppressive and/or biological therapy. Furthermore, patients in remission at 1 year are very likely to remain in remission at 2 years also, explaining why colonoscopy is thus not mandatory at year 2. Imaging techniques (CT, MRI) were considered of uncertain appropriateness for disease monitoring in remission, probably because they do not allow direct assessment of the mucosa.

For patients in remission treated with azathioprine, 6-MP or methotrexate, treatment discontinuation was considered appropriate and safe after 4 years. It was agreed that this decision could easily be taken if the patient was in deep remission. In the case of biological therapy, the experts considered stopping therapy appropriate after 4 years but also after 2 years if the patient was in deep remission. This may seem surprising as the mean duration of biological therapy reported in the study by Louis et al. was only 2.2 years, while relapse occurred in 50% after the stop of infliximab. The experts' decision to consider that benefits exceeded risks was guided not only by the aforementioned evidence but also by considerations such as quality of life for not being under the constraint of following a therapy, side effects, reducing the risk of treatment's untoward consequences and the high response rate (88%) of relapsing patients if therapy needs to be resumed.[14] There were no major differences in the judgement to stop therapy, whether patients had undergone prior CD-related surgery or not.

In conclusion, stopping immunosuppressive, biological or combined therapy in CD patients with deep clinical, biological and endoscopic remission was judged to be justified for all treatment categories after 4 years. Known risk factors for relapse after therapy withdrawal[12,14] allow the clinician to optimize this decision in individual cases. The high response rate after reintroduction of therapy in the event of relapse, the significant cost of biological therapy and the side effect profile of immunosuppressive and biological therapy are likely to be the major determinants in decision making. This study highlights a new concept, i.e., the most appropriate time interval before stopping therapy in patients with deep remission. The safety and actual risk/benefit ratio of therapy withdrawal needs to be studied in prospective controlled trials, given the need to optimize the use and duration of potentially risky and costly therapies.

Acknowledgments

This study was carried out by all the gastroenterologists and investigators listed in Appendix A. The study is supported by the Swiss National Science Foundation (SNSF) grants no. 33CS30-134274 (Swiss IBD cohort study) and 32473B-138498 (Appropriateness of care in IBD).

Statement of authorship: study design and conception (VP, FF, MM, CM, JJG, CF, JPV, BB, PM, AS), statistical analysis (VP), analysis and interpretation (VP, FF, MM, CM, JJG, JPV, BB, PM, AS), drafting the article or revising it critically for important intellectual content (VP, FF, MM, CM, JJG, CF, JPV, BB, PM, AS), final reading and approval of the manuscript (VP, FF, MM, CM, JJG, CF, JPV, BB, PM, AS).

Appendix A. The EPACT-II-Update panellists

Dr. Erika Angelucci (Italy), Prof. Willem A. Bemelman (The Netherlands), Prof. Bruno Bonaz (France), Prof. Peter Lakatos (Hungary), Prof. Milan Lukas (Czech Republic), Prof. Gerassimos Mantzaris (Greece), Prof. Colm O'Morain (Ireland), Prof. Tom Öresland (Norway), Prof. Laurent Peyrin-Biroulet (France), Prof. Bernhard Sauter (Switzerland).

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