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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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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.

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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.