Journal of Crohn's and Colitis (2009) 3, 241–249

available at www.sciencedirect.com

Appropriate maintenance treatment for Crohn's disease: Results of a multidisciplinary international expert panel — EPACT II

Pascal Juillerat[a,b,*], John-Paul Vader[b], Christian Felley[a], Valérie Pittet[b], Jean-Jacques Gonvers[a], Christian Mottet[a], Willem A. Bemelman[c], Marc Lémann[d], Tom Öresland[e,f], Pierre Michetti[a], Florian Froehlich[a,g] and the EPACT II Study Group [1]

[a] *Department of Gastroenterology & Hepatology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland*
[b] *Healthcare Evaluation Unit, Institute of Social & Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland*
[c] *Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands*
[d] *Department of Gastroenterology, Hôpital Saint-Louis, Paris, France*
[e] *Faculty Division, Akershus University Hospital, University in Oslo, Oslo, Norway*
[f] *Department of GI Surgery, Akershus University Hospital, Lørenskog, Norway*
[g] *Department of Gastroenterology, University of Basle, Basle, Switzerland*

Received 13 March 2009; received in revised form 13 May 2009; accepted 13 May 2009

KEYWORDS
Crohn's disease;
Therapy;
Maintenance treatment;
Appropriateness;
RAND Appropriateness Method;
Inflammatory bowel disease

Abstract

Introduction: Biological therapy has dramatically changed management of Crohn's disease (CD). New data have confirmed the benefit and relative long-term safety of anti-TNFα inhibition as part of a regular scheduled administration programme. The EPACT appropriateness criteria for maintenance treatment after medically-induced remission (MIR) or surgically-induced remission (SIR) of CD thus required updating.
Methods: A multidisciplinary international expert panel (EPACT II, Geneva, Switzerland) discussed and anonymously rated detailed, explicit clinical indications based on evidence in

Abbreviations: CD, Crohn's Disease; 5-ASA, mesalazine and other aminosalicylates; AZA, azathioprine; 6MP, 6-mercaptopurine; MTX, methotrexate; TNFα, Tumor Necrosis Factor alpha; MIR, Medically-Induced Remission; SIR, Surgically-Induced Remission; RCT, Randomized Controlled Trial; ECCO, European Crohn's & Colitis Organization; AGA, American Gastroenterological Association.

* Corresponding author. Pascal Juillerat, MD c/o Professor Pierre Michetti, Department of Gastroenterology & Hepatology, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland. Tel.: +41 21 314 0690; fax: +41 21 314 0707.
E-mail address: pascal.juillerat@chuv.ch (P. Juillerat).

[1] The EPACT II Study Group (in alphabetical order): Erika Angelucci (Italy), Willem Bemelman (The Netherlands), Miquel Gassull (Spain), Franz Josef Heil (Germany), Marc Lémann (France), Tom Öresland (Norway), Colm O'Morain (Ireland), Yves Panis (France), Frank Seibold (Switzerland), Eduard Stange (Germany), Reinhold Stockbrügger (The Netherlands) and Boris Vucelic (Croatia).

1873-9946/$ - see front matter
doi:10.1016/j.crohns.2009.05.002

the literature and personal expertise. Median ratings (on a 9-point scale) were stratified into three assessment categories: appropriate (7–9), uncertain (4–6 and/or disagreement) and inappropriate (1–3). Experts ranked appropriate medication according to their own clinical practice, without any consideration of cost.
Results: Three hundred and ninety-two specific indications for maintenance treatment of CD were rated (200 for MIR and 192 for SIR). Azathioprine, methotrexate and/or anti-TNFα antibodies were considered appropriate in 42 indications, corresponding to 68% of all appropriate interventions (97% of MIR and 39% of SIR). The remaining appropriate interventions consisted of mesalazine and a "wait-and-see" strategy. Factors that influenced the panel's voting were patient characteristics and outcome of previous treatment. Results favour use of anti-TNFα agents after failure of any immunosuppressive therapy, while earlier primary use remains controversial.
Conclusion: Detailed explicit appropriateness criteria (EPACT) have been updated for maintenance treatment of CD. New expert recommendations for use of the classic immunosuppressors as well as anti-TNFα agents are now freely available online (www.epact.ch). The validity of these criteria should now be tested by prospective evaluation.

1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel condition which can involve any part of the digestive tract, but is predominantly located in the terminal ileum and the colon [1]. No cure is currently available for CD and the principal therapeutic issues are thus the management of frequent relapses (induction of remission) and the stabilisation of this state thereafter by continuous medication (maintenance treatment). The available evidence on maintenance therapy after medically-induced remission (MIR) and surgically-induced remission (SIR) has been reviewed in previous articles. [2,3]

For the maintenance of MIR, treatment and interventions that have demonstrated efficacy are smoking cessation and immunomodulatory drugs. The efficacy of azathioprine and 6-mercaptopurine (AZA/6MP) has been demonstrated in many controlled trials and in two meta-analyses. [4,5] An RCT on the use of intramuscular methotrexate (MTX) showed a significant benefit over placebo for long-term maintenance of remission, [6] which is also supported by recent results at 50 weeks in the COMMIT trial. [7] Nevertheless, MTX teratogenicity imposes postponement of conception and pregnancy. Budesonide, probiotics, antibiotics and natalizumab are described but data from the published literature are unconvincing and/or controversial: Three meta-analyses deal with budesonide, the most recent of which analysed 4 RCTs and reported a dose-related effectiveness with an increase in duration of disease-free time not exceeding one year, which was confirmed by a recent trial by Hanauer et al. [8] Mesalazine (5-ASA) is not efficient for maintenance of MIR according to the recently-published Cochrane review. [9] Lastly, medication which influences the bioflora (antibiotics or probiotics) was not considered conclusive, probably because of the weakness of the existing studies. Placebo-controlled data on the anti-α4 integrin antibody natalizumab were conclusive versus placebo after 60 weeks' maintenance therapy according to the ENACT trial [10] (428 patients). There are, however, concerns about its potential association with progressive multifocal encephalopathy. [11] Steroids and cyclosporine are not effective for this indication and no data exists for tacrolimus, mycophenolate mofetil and cyclophosphamide. Most recently-published studies devoted to anti-tumor necrosis factor (TNF) α agents described long-term maintenance after open-label induction: one maintenance trial with infliximab [12] and the ACCENT I [13] (infliximab, 54 weeks), CLASSIC II, [14] CHARM [15,16] (adalimumab, 56 weeks) and PRECiSE 2 (certolizumab, 26 weeks) [17] studies. These studies were analyzed in a Cochrane review [18] and their follow-up presented at recent international meetings. [19,20] Infliximab in a scheduled administration infusion programme has been shown to induce a reduction in immunogenicity and related delayed reactions [12,21] and a recent meta-analysis confirmed its relative safety. No difference was found in 21 RCTs between anti-TNFα agent groups and control groups with respect to death, malignancy and serious infections, [22] which corresponded to analyses of the TREAT registry. [23] Each immunosuppressed patient may be at risk of acquiring infections, particularly opportunistic infections, while under combination therapy (anti-TNFα agents and immunosuppressors). [24] Long-term safety remains to be evaluated. In contrast to published data on rheumatoid arthritis, there is no clear clinical benefit of a combination therapy on clinical outcome according to the IMID (Infliximab Maintenance Immunosuppression Discontinuation) trial. [25] In this study, combined therapy resulted in a decrease in CRP level and an increase of infliximab serum levels. Some cases of hepato-splenic lymphoma [26,27] have been described in young, predominantly male, patients under combination therapy with azathioprine and infliximab. Based on these recent data, combination therapy should thus not be continued for more than 6 months. One study discussed a treatment paradigm: "Should we use anti-TNFα as first-line (top–down) therapy or pursue a traditional (step-up) therapy". According to a European and a North American panel of experts, the top–down approach should not be used routinely for luminal CD, but can be considered for use in patients with extensive and, in particular, fistulizing disease. [28] Finally, the first RCTs comparing infliximab, azathioprine and combination treatment in naïve patients have recently shown a significant beneficial effect of infliximab and combined therapy compared to azathioprine