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

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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

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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. 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.

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. An RCT on the use of intramuscular methotrexate (MTX) showed a significant benefit over placebo for long-term maintenance of remission, which is also supported by recent results at 50 weeks in the COMMIT trial. 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 are described but data from the published literature are controversial: Three meta-analyses have recently shown a significant beneficial effect of infliximab and combined therapy compared to azathioprine. 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 and the ACCENT I (infliximab, 54 weeks), CLASSIC II, (adalimumab, 56 weeks) and PRECISe 2 (certolizumab, 26 weeks) studies. These studies were analyzed in a Cochrane review and their follow-up presented at recent international meetings. infliximab in a scheduled administration infusion programme has been shown to induce a reduction in immunogenicity and related delayed reactions and a recent meta-analysis confirmed its relative safety. No difference was found in 21 RCTs between anti-TNF-α agents and immunosuppressors as well as anti-TNF-α agents are now freely available online (www.epact.ch). The validity of these criteria should now be tested by prospective evaluation.

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alone. This provides further evidence for a “top-down” treatment approach for active disease, which later influences remission maintenance.

For postoperative maintenance treatment, an updated meta-analysis demonstrated benefit from mesalazine (>2 mg/d), with a number needed to treat between 6 and 12. 5-ASA is considered as a first option for patients with low risk of relapse. In high-risk patients, according to most review articles, thiouporines are the first-choice therapy, although only four studies (2 RCTs and 2 case series) on AZA/6MP have been published. Finally, nitromidazol (metronidazole or ornidazole) were shown to be effective in patients after isolated ileal resection. Concerns on toxicity restricted their use in the long term, however. A useful alternative may be a combined treatment with azathioprine and metronidazole, which demonstrated maintenance of endoscopic remission. Prednisone, budesonide, probiotics and IL-10 were considered ineffective. Many issues regarding postoperative maintenance therapy of Crohn's disease remain unresolved and there is a need for high-quality data, in particular for methotrexate, anti-TNF agents and natalizumab. Regueiro et al. published the first RCT on biologicals in the postoperative setting. Twenty-three CD patients post-ileo-caecal resection were randomized to infliximab and placebo, with a 1-year endoscopic remission maintained in 90% of the patients with infliximab (vs 15.4% for placebo).

The second European Panel on the Appropriateness of Crohn’s Disease Therapy (EPACT II) convened in Geneva, Switzerland in December 2007. Twelve experts (8 gastroenterologists, 1 internist/general practitioner and 3 surgeons), from 9 European countries (Croatia, France, Germany, Ireland, Italy, Spain, Sweden, Switzerland and the Netherlands) participated in the panel. Based on an initial panel, which took place in Lausanne, Switzerland in 2004 (EPACT I), EPACT II aimed to update and redefine appropriateness criteria for the treatment of Crohn’s disease, according to recent advances in medicine and new evidence from the published literature. This article focuses on the appropriateness of maintenance therapy for surgically- or medically-induced remission and compares these results to the ECCO consensus, EPACT I and to the published literature.

2. Method

The RAND Appropriateness Method is a well-recognized means of standardizing expert opinion and comprises an evidence-based review of the literature, a panel meeting and a voting process. Methodological details are fully described in an earlier article on the results of EPACT I and in the literature review of this panel.

Based upon the literature review, MIR and SIR maintenance therapy was defined as well as factors which could influence medical decision-making (Table 1). Mini-clinical scenarios corresponding to daily practice were created. During the first round of the panel, these clinical indications were voted on by the experts by mail and any discrepancies or other questions were discussed in depth with the organizers during scheduled telephone conference calls. This step was aimed at preparing the meeting, correcting any discrepancies but not to solve them. All such discrepancies were discussed face to face at the panel meeting (before the second rating of the clinical situations).

In order to have the most clinically-oriented approach, if several drugs were appropriate for the same clinical situation experts were asked to classify their choice from the most (A) to the least appropriate drug (B, C, D or E, according to the number of appropriate drugs). On this basis, a ranking was obtained by accumulation of points: an A representing 2 points; a B 1 point and with no points being given for C, D, E.

A treatment is defined as being appropriate in a situation where the benefit to the patient exceeds the potential risks by a sufficiently wide margin that the treatment is worth giving. The panel rated the appropriateness of various interventions, represented in Figs. 1 and 2. The definitions of all interventions (treatments or surgery) were previously defined (before rating) for the experts and were available at the panel meeting.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>EPACT II definitions.</th>
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<tbody>
<tr>
<td><strong>Maintenance of medically-induced remission of luminal Crohn’s disease.</strong></td>
<td></td>
</tr>
<tr>
<td>Assumption (for all indications)</td>
<td></td>
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<tr>
<td>If remission was obtained with biologicals (infliximab, adalimumab, certolizumab), this implies steroid failure, or intolerance.</td>
<td></td>
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<tr>
<td>Remission (= quiescent disease)</td>
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<tr>
<td>Clinical remission (CDAI &lt; 150), possibly confirmed by endoscopy, refers to patients who are asymptomatic and without inflammatory sequelae and includes patients who have responded to acute medical intervention.</td>
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<tr>
<td>Relapse</td>
<td></td>
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<tr>
<td>Defined as both a CDAI &gt; 150 points and a minimum increase of the baseline CDAI score (&gt;70 points). Relapse is a clinical definition whereas recurrence means the presence of lesions.</td>
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<tr>
<td>• Low frequency of relapses: ≤ 1 flare per year</td>
<td></td>
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<tr>
<td>• High frequency of relapses: &gt; 1 flare per year</td>
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**Maintenance of surgically-induced remission of luminal Crohn’s disease.**

 Preventing relapse in patients who have undergone surgical resection without gross evidence of residual disease. Evaluation of flare's prognosis based on the classification of high and low risk of recurrence, according to the risk factors listed if any of the following apply:

<table>
<thead>
<tr>
<th>High risk</th>
<th>Low risk</th>
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<tbody>
<tr>
<td>&gt; 2 Prior CD operations</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>YES Previous resection &gt; 1 m</td>
<td>NO</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Ileocolonic disease</td>
<td></td>
</tr>
<tr>
<td>Perianal disease</td>
<td></td>
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<tr>
<td>Severe lesion at endoscopy (at about 6–12 months)</td>
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**Comment**: Some evidence suggests that females have a higher relative risk of relapse.

• *Watchful waiting* (= “wait-and-see”) Follow up the course of the disease clinically and/or endoscopically, in the absence of any maintenance therapy, at least every 6–12 months.
Smoking was not voted on by the experts as they all agreed that smoking cessation was appropriate in all situations. The level of appropriateness of a specific intervention in each clinical indication was calculated using any time during the panel procedure. They have also been published with the literature review in a companion article on drug safety, and are freely available on our website (www.epact.ch).
Figure 2 Appropriateness ratings of therapy for maintenance of surgically-induced remission of Crohn’s disease.

AZA/6MP = Azathioprine / 6 Mercaptopurine; MTX = Methotrexate; 5-ASA = 5-aminosalicylic Acid

THERAPY RANK:
(1): 1st line therapy - (2): 2nd line therapy - (3): 3rd line therapy
the median value of the twelve experts’ votes between 1 and 9 (1 = extremely inappropriate, 9 = extremely appropriate). According to the values thus obtained, each scenario was classified as "appropriate", "uncertain" or "inappropriate" (1–3 = inappropriate; 4–6 = uncertain; 7–9 = appropriate). In a classical interpretation of the results, an intra-panel disagreement was considered to be present when at least three of the twelve ratings fell in the 1–3 category and at least three others in the 7–9 point category. This situation was then defined as "uncertain", irrespective of the median panel score. Finally, the IPRAS (InterPercentile Range Adjusted for Symmetry) method of analysis allowed a reduction of the number of disagreements in the experts’ votes by more adequately measuring the degree of dispersion between ratings.

3. Results

Panelists voted on 362 clinical situations relevant to maintenance treatment of Crohn’s disease (200 scenarios for MIR by steroids and 162 scenarios for SIR, which corresponded to 35% of all the 1024 clinical scenarios developed for the panel as a whole). One in six of the proposed interventions (62 scenarios) was considered inappropriate. The same number were uncertain, whereas two-thirds (238 scenarios) were considered inappropriate. The drugs considered appropriate were AZA/6MP, MTX or anti-TNFα agents in 42 clinical scenarios, which corresponded to 68% of all appropriate indications (97% of MIR and 39% of SIR scenarios). The remaining interventions were allocated to a “wait-and-see” strategy (3% of MIR and 23% of SIR) and 5-ASA, (19%, exclusively for SIR).

For maintenance of medically-induced remission of Crohn’s disease, the panel rated the appropriateness of treatment by 5-ASA, budesonide, prednisone, AZA/6MP, probiotics, MTX, infliximab, adalimumab, certolizumab andnatalizumab. In the postoperative setting, two drugs (budesonide and probiotics) were not taken into consideration due to a lack of evidence, and antibiotics were added to the evaluation. Medical attitudes such as “wait-and-see” and “quit smoking” were also taken into consideration. Finally, smoking was not voted on as all the agreed that in all situations smoking cessation was appropriate.

3.1. Maintenance of medically-induced remission of Crohn’s disease obtained by steroids (Fig. 1)

The induction treatment with steroids considered here was defined as prednisone 40 to 60 mg (1–1.5 mg/kg/d) or equivalent, or budesonide 9 mg/d for at least 2 weeks and then tapered to give the shortest possible treatment in order to avoid adverse events.

In low-frequency relapse patients, two clinical scenarios are appropriate: AZA/6MP for first-line therapy and “wait-and-see” as second-line therapy, whereas MTX was considered uncertain. All other drugs are considered inappropriate (5-ASA, budesonide, infliximab, probiotics, adalimumab, certolizumab, natalizumab).

In high-frequency relapse patients, maintenance therapy always seems to be appropriate and AZA/6MP were rated as first-line drugs. After AZA/6MP failure, MTX was the drug of choice if it had never been used before or was previously successful. There was a disagreement on infliximab and adalimumab, which were considered to be uncertain, if methotrexate had not already been tried. However, when MTX failed, the experts’ votes proposed the use of infliximab and then adalimumab, but there was disagreement on use of certolizumab.

3.2. Maintenance of medically-induced remission of Crohn’s disease obtained by biologicals (Fig. 1)

Patients with low-frequency relapses were considered to be maintained in remission with AZA/6MP, whereas infliximab use was controversial (uncertain, with disagreement). MTX and the “wait-and-see” attitude were considered uncertain. All other drugs were inappropriate.

In patients with high-frequency relapses, when AZA/6MP was previously successful or not/never given, it was considered appropriate independently of the result of prior use of methotrexate. Both immunosuppressors were, however, considered inappropriate once they had failed.

According to the experts’ votes, the best approach was to use biologicals in patients with a high-frequency relapse rate after failure of AZA/6MP and MTX (see right side of Fig. 1). The result of the ranking was: first, infliximab (score of 8), then adalimumab (score of 7), whereas the panelists disagreed on certolizumab. For all other clinical scenarios when one of the classical immunosuppressors (AZA/6MP or MTX) was not/never given or previously successful, the use of biological treatment for maintenance of remission was uncertain or even controversial (disagreement). At this time, a “wait-and-see” attitude was not recommended and all of the following treatments were inappropriate: 5-ASA, antibiotics, budesonide, infliximab, probiotics, natalizumab.

3.3. Maintenance treatment of surgically-induced remission of Crohn’s disease (Fig. 2)

In low-risk patients, 5-ASA compounds were judged to be appropriate if there was no prior failure with this drug. However, the “wait-and-see” strategy was rated the first-line therapy when the patient was naive to maintenance treatment or if there was prior failure with 5-ASA and AZA/6MP. Finally, AZA/6MP was chosen if there had been prior success with this therapy and was certain in naïve patients.

In high-risk patients, AZA/6MP were predominantly the first choice of the experts if there was no prior thiopurine failure. In this situation, their second choice was the use of 5-ASA, if this drug had not been given or was successful in the past, followed by MTX. In all other situations in postoperative patient management, MTX as well as antibiotics were considered uncertain, whereas the following treatments were inappropriate for all indications: infliximab, adalimumab, certolizumab, natalizumab.

4. Discussion

This article describes a panel update on maintenance treatment of Crohn’s disease considering medically- and
Appropriate maintenance treatment for Crohn’s disease

surgically-induced remission separately. The panel criteria are based on expert opinion (RAND panel process), without consensus. Explicit clinical scenarios submitted to the experts were based on factors which were relevant to clinical decision-making in daily clinical practice. The RAND Appropriateness Method does not, however, take health insurance or public health pressures or healthcare costs into consideration and these may vary from one country to another. For this reason, appropriateness criteria have to be interpreted and applied with respect to the financial and societal aspects of the local health system in which they are intended to be used.

In medically-induced remission (MIR), azathioprine/6-mercaptopurine (AZA/6MP) was mainly considered as the primary therapy, whereas 5-ASA compounds were clearly inappropriate, which corresponded to the evidence from the literature. 

In case of prior failure with thiopurines, methotrexate, infliximab and adalimumab were appropriate in order of preference and appropriateness was then influenced by the successive failures of these previous therapies. There was uncertainty concerning the continuation of infliximab after induction in low-risk patients. This attitude remains controversial in the absence of relevant studies and in view of ACCENT I and a recent publication based on the experience of a centre of reference (Leuven), which suggest that infliximab could be discontinued without provoking relapse in some patients. When analyzing appropriate results only, there was, however, almost no difference between patients in whom remission was induced by steroids or by biological drugs (the only exception was a "wait-and-see" strategy suggested as a second choice in naive patients of the first group). These two remission strategies prefigured a "top-down" treatment approach with infliximab, which was later published (SONIC trial) and confirm that the question of how to maintain remission after treatment with anti-TNFα agents is crucial, in particular because there are obvious safety concerns with combined therapy (anti-TNFα agents and immunosuppressors).

For this reason, maintenance treatment with biologicals was actively debated at EPACT II, and the second round of the panel process was not able to clarify some uncertainties despite the presence of more evidence on the long-term safety of these drugs. Methotrexate (MTX), which has a longer history of use and thus a better risk-benefit ratio, was in many situations considered as more appropriate than anti-TNFα agents in the absence of any currently available comparative studies. This could possibly explain the fact that after azathioprine failure only, the appropriateness of the use of infliximab and adalimumab was still uncertain.

Corticotizumab was always considered uncertain in the situations described above, certainly due to the fact that at this time no FDA (Food and Drugs Administration) and EMEA (European MEdicines Agency) approval for this medication has been granted. In conclusion, according to the panel, the best indication for use of anti-TNFα agents in medically-induced remission seems to be failure of both of the conventional immunosuppressive therapies (AZA/6MP and MTX). Combined therapies (infliximab with AZA/6MP or MTX) were not rated by the panel.

In surgically-induced remission (SIR), AZA/6MP was also considered the primary therapy, achieving higher ratings and agreement scores, in particular for high-risk patients. In case of previous failure with AZA/6MP, the experts’ votes suggest the use of 5-ASA and, if needed, of MTX. In low-risk patients, 5-ASA was the most appropriate drug for use in the postoperative setting, which corresponds to one of the few pieces of strong evidence from the published literature. 

Although there is no clear evidence to determine which dose should be used, the experts voted on a standard dose of mesalazine of between 3.2 and 4 g/day. From a global point of view, it is interesting to underline the high appropriateness scores of "less aggressive" treatments (5-ASA, "wait-and-see" strategy) in patients who have undergone surgery at least once and who therefore are at high risk of relapse. This suggests considerable uncertainty in the postoperative setting and the use of the "wait and see" strategy. However, this attitude is still mentioned in review articles. The first use of anti-TNFα agents in this setting suggests a promising future, but additional investigation is required.

The European Crohn’s & Colitis Organization (ECCO) consensus panel convened in 2005. Comparison of EPACT II to ECCO guidelines is, however, difficult in some situations because EPACT II clinical scenarios evaluate the sequence of treatment in more detail (failure of one or two previous drugs, ranking); our results are globally consistent with most ECCO statements for both MIR or SIR maintenance treatment.

In MIR maintenance treatment with 5-ASA, points of view differ: according to the EPACT panel all votes classified this drug as inappropriate, whereas after a first presentation, ECCO experts considered 5-ASA as a treatment option (Statement 6A). In SIR maintenance treatment, the ECCO consensus added that 5-ASA and imidazole in low-risk patients can be proposed after small intestine resection and ileocolic resection, respectively (Statement 8F). Consensus members also mentioned that the latter is not frequently used because of significant side-effects. On this specific point, the EPACT panel did not differentiate between the type of surgery or the location of the disease prior to surgery and this may be why the panelists rejected the use of antibiotics.

The American Gastroenterological Association (AGA) biologicals conference took place in June 2006 with a panel composed of inflammatory bowel disease experts from Europe and North America. They defined an anti-TNFα maintenance treatment (infliximab, adalimumab, certolizumab) as indicated if remission occurred under biological treatment. The AGA Institute medical position statement on corticosteroids, immunosuppressants and infliximab in inflammatory bowel disease published similar recommendations. In a recent review article, Sandborn et al reported the same considerations as EPACT concerning immunomodulators, but added two points associated with maintenance in MIR: first, 5-ASA in clinical practice is widely used despite the lack of evidence and second, budesonide prolongs the time to relapse for a 6-month period but is inefficient for more than a one-year duration.

Between the first (EPACT I) and the second RAND panel (EPACT II), the number of scenarios assessed increased more than threefold (90 in MIR and 12 in SIR for EPACT I versus 200 and 162 indications for EPACT II, respectively), reflecting a higher degree of complexity in decision-making and the increase in therapeutic options available. Compared to EPACT I, there is a trend towards a more aggressive
treatment in MIR maintenance therapy (appropriate use of AZA/6MP even in patients with low risk of relapse). For SIR treatment, the major change in the EPACT II panel was the addition of methotrexate, a new drug for this indication, which was rated appropriate in high-risk patients. Despite the need to improve the impact of postoperative maintenance treatment, there are still no clear-cut indications for anti-TNFα agents in this setting of high risk of relapse, probably due to a lack of solid scientific data.

5. Conclusion

Detailed explicit appropriateness criteria have been updated for maintenance treatment of CD and are now freely available online (www.epact.ch).

These criteria are particularly useful for targeting the practical use of immunomodulators and anti-TNFα agents. The validity of these criteria should now be prospectively evaluated.

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