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Appropriateness of therapy for active Crohn's disease: Results of a multidisciplinary international expert panel—EPACT II

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Abstract

The increasing number of trials testing management strategies for luminal Crohn's disease (CD) has not filled all the gaps in our knowledge and thus, in clinical practice, many decisions for CD patients have to be taken without the benefit of high-quality evidence.
Methods: A multidisciplinary European expert panel used the RAND Appropriateness Method to develop and rate explicit criteria for the management of individual patients with active, steroid-dependent (ST-D) and steroid-refractory (ST-R) CD.
Results: Overall, 296 indications pertaining to mild-to-moderate, severe, ST-D, and ST-R CD were rated. In anti-TNF naïve patients, budesonide and prednisone were found to be appropriate for mild-moderate CD, and infliximab (IFX) was appropriate when these had previously failed or had not been tolerated. In patients with a prior successful treatment by IFX, this drug, with or without co-administration of a thiopurine analog, was favoured. Other anti-TNFs were

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appropriate in the presence of intolerance or resistance to IFX. High-dose steroids, IFX or adalimumab were appropriate in severe active CD. For the 105 indications for ST-D or ST-R disease, the panel considered the thiopurine analogs, methotrexate, IFX, adalimumab, and surgery for limited resection, to be appropriate, depending on the outcome of prior therapies. Anti-TNFs were generally considered appropriate in ST-R.
Conclusion: Steroids, including budesonide for mild-to-moderate CD, remain the first-line therapy for active luminal CD. Anti-TNFs, in particular IFX as shown by the amount of available evidence, remain the second-line therapy for most indications. Thiopurine analogs, methotrexate and anti-TNFs are favoured in ST-D patients and ST-R patients.

1. Introduction

Crohn's disease (CD), a chronic inflammatory bowel disease, is a condition which may involve any part of the gastrointestinal tract, but most commonly affects the terminal ileum and the colon. CD patients' quality of life was directly related to disease activity and was worse in active disease than in remission,[1] which is why appropriate treatment is of importance. Several factors influence the choice of therapy, including disease location, disease severity, response to prior therapies, and the occurrence of adverse reactions to these prior therapies. Disease severity is evaluated based on the American College of Gastroenterology's (ACG) criteria.[2]

Mild-to-moderate CD, as defined by ACG criteria, refers to ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity, abdominal tenderness, painful mass, obstruction, or weight loss in excess of 10%. In these patients, two large and rigorous studies have shown that sulfasalazine (SFS) is modestly effective in inducing remission of CD,[3,4] while mesalazine failed to induce any substantial clinical benefit over placebo, as shown by a meta-analysis.[5] Systemic steroids can induce remission in mild-to-moderate CD, but are associated with numerous side-effects. In clinical trials, budesonide showed a better safety profile and an efficacy similar to that of conventional steroids in patients with mild-to-moderate CD,[6,7] even if, in a meta-analysis, the efficacy of budesonide, as compared to conventional steroids, was found to be inferior in patients with high CDAI scores.[8] Finally, antibiotics, although widely used in practice, have not shown any proven efficacy in inducing remission, although rigorous studies are still lacking.

Moderate-to-severe CD, according to the ACG's criteria, applies to patients who have failed to respond to treatment for mild-to-moderate disease or those with more prominent symptoms such as fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia. The efficacy of oral corticosteroids in inducing remission in this group of patients has been established by the results of two large multicenter randomized trials.[3,4] Over time, however, a substantial proportion of patients develop side-effects, resistance to and/or dependence on steroids, underlining the need for alternative therapies.[9,10] For patients with moderate-to-severe CD who develop side-effects or resistance to steroids, infliximab, a monoclonal chimeric antibody to TNF, is a well-studied alternative to steroids.[11–14] Other anti-TNF agents, such as adalimumab and certolizumab pegol, have also been shown to be effective in the same groups of patients.[15–23] These subcutaneous anti-TNFs tend, however, to have a slower onset of action than infliximab, an aspect which is relevant when treating patients with more active or severe disease. A Cochrane collaboration analysis of four studies confirmed the potential of natalizumab, an anti-alpha 4-integrin antibody, to induce remission in patients with moderate-to-severe active CD, but the potential risk of progressive multifocal encephalopathy has prevented its registration for CD treatment.[24] The use of an elemental or polymeric diet, evaluated in three meta-analyses, was judged to be less effective than steroids in inducing remission in adult CD patients, without any difference being made between these two types of liquid foods.[25–27] Finally, surgery with a conservative approach should be considered for patients with risk factors or contraindications to medical therapy and limited disease.

The management of patients with *steroid-dependent* (ST-D) or *steroid-refractory* (ST-R) CD frequently relies on the use of the purine analogues azathioprine and 6-mercaptopurine (AZA/6-MP), as shown by eight controlled trials and a meta-analysis that demonstrated their efficacy in patients with ST-R disease.[3,28–34] Methotrexate (MTX), a blocker of folate metabolism with immunosuppressive properties, has been evaluated in three randomized placebo-controlled trials. Two studies showed no efficacy in ST-D or ST-R CD patients,[35,36] while the third study demonstrated a benefit with a significant decrease in steroid use in these patients.[37] Infliximab, as well as adalimumab, has also shown a steroid-sparing effect in ST-R patients.[13,18,38–41] Finally, surgery may be considered in severe, refractory disease, when resection is feasible.[42]

Despite the evidence briefly summarized above, but reviewed in detail as an integral part of the RAND Appropriateness Method earlier,[43,44] treatment decisions remain difficult in practice, as data that would directly apply to patients are lacking, or because direct comparison trials between the various possible therapeutic options have not been conducted.

The second European Panel on the Appropriateness of Crohn's Disease Therapy (EPACT II) convened in Geneva, Switzerland in December 2007, with the aim of defining practical approaches to the treatment of CD patients using the RAND methodology. The expert panel included 12 experts (8 gastroenterologists, 1 internist/GP and 3 surgeons) from nine European countries (Croatia, France, Germany, Ireland, Italy, Spain, Sweden, Switzerland, and The Netherlands) who were brought together to update and expand the 3 year-old EPACT appropriateness criteria for the treatment of CD, in the light

of recent advances in the published literature. The present report focuses on the results of the panel's work with respect to the appropriateness criteria for the treatment of active luminal, as well as of ST-D and ST-R forms of the disease.

2. Methods

The RAND Appropriateness Method (RAM) has been used to standardize expert opinion concerning the appropriateness of diagnostic and/or therapeutic interventions in a given field of medicine. It combines evidence from the medical literature and the personal clinical experience of experts in the field in a predefined 3-step approach that includes firstly a detailed review of all relevant original data in the literature, followed by an expert panel meeting and, finally, a voting process by all the experts on precise clinical scenarios reflecting the widest possible range of clinical situations. The RAM is one of the most highly appreciated methods of judging appropriateness of clinical interventions.[45] The methodological details of the RAND method, as applied to the EPACT project, are fully described in previous publications.[46,47]

An international multidisciplinary panel of 12 experts convened in Switzerland in December 2007 to rate the appropriateness of explicit clinical scenarios of CD corresponding to daily practice. The goal was to intensively evaluate the multiple scenarios. The experts were chosen to represent all parts of Europe and to gather together the expertise from gastroenterologists, visceral surgeons and primary care physicians interested in the care of IBD patients. Each panel member had to be nominated by his/her national IBD group or specialty society to represent his/her country in this panel. Most of the gastroenterologists were in fact active ECCO National Representatives of their country.

Based upon the literature review provided to the panelists and an initial contact with the experts, therapies for mild-to-moderate, severe, ST-D and ST-R were defined and factors influencing clinical decision were identified.

A treatment is defined as being appropriate in a situation when the benefit to the patient exceeds the potential risks by a sufficiently wide margin that the treatment is worth giving.[48] For active CD, including ST-D and ST-R, 294 clinical situations, corresponding to the indication for one drug in one clinical setting, were identified. The EPACT panel experts were first asked to individually rate, on a 9-point scale (1=extremely inappropriate, 9=extremely appropriate), the appropriateness of each of these drug indications (scenarios) based on the evidence in the literature (the complete literature review was provided to them at this stage) and on their own clinical expertise and experience, prior to the panel meeting. The median value of their votes was then computed for each specific scenario and stratified into three categories: appropriate (7–9), uncertain (4–6) and inappropriate (1–3). If an intra-panel disagreement situation occurred, as defined by three or more of the 12 ratings in the inappropriate category and three others in the appropriate category, the scenario was deemed uncertain, regardless of the median score. During the panel meeting, these preliminary scores were discussed, scenarios modified as necessary, and a second, final, individual vote performed. The medians of this vote were computed to define the appropriateness of each scenario as detailed above.

In situations where a panelist would rank more than one drug as appropriate in a given scenario, he was asked to further rank all the appropriate drugs from the best-choice (given the letter A) to the least-fitting drug (B, C, D, …), according to the number of appropriate choices in the given clinical situation.

3. Results

Panelists rated 294 clinical situations related to active CD, including 167 scenarios for mild-to-moderate, 22 for severe, 45 scenarios for ST-D, and 60 scenarios for ST-R disease. These together represented 29% of the total of 1024 scenarios submitted to the panel. Overall, 101 scenarios (34% of the 294 clinical presentations) were considered appropriate, 76 were uncertain (26%) and 117 inappropriate (40%). Details of all ratings are given in the figures contained in this article, the paragraph below thus only highlighting the most relevant general results.

3.1. Mild-to-moderate active luminal Crohn's disease

In *anti-TNF naïve patients*, budesonide and prednisone were considered appropriate, with a preference for the first cited unless this treatment had previously failed, whereas sulfasalazine and 5-ASA were rated as uncertain. The panel assumed that budenoside was to be used only in cases were disease location would be limited to the ileum and/or right colon. More aggressive approaches, such as AZA/6MP, MTX, IFX, adalimumab, certolizumab pegol and Natalizumab, were all considered inappropriate. In the event of a prior failure of steroids, the experts rated IFX as the first-choice therapy and AZA/6MP and MTX as subsequent appropriate solutions. Adalimumab was rated uncertain in the event of steroid failure.

In *patients previously treated by IFX*, this drug, prednisone and AZA/6MP were found to be appropriate in the event that this drug has been used successfully before. Adalimumab was mostly rated appropriate after IFX failure, intolerance or loss of response. Surgery was deemed appropriate for ileo-caecal disease if both steroids and anti-TNF had proven to be ineffective. In the case of previous IFX failure or loss of response, there was uncertainty regarding the appropriateness of increasing the dose, the panel favoring a switch to adalimumab, or the use of prednisone in patients previously naïve to steroids or having shown response to them. In this situation, certolizumab pegol remained rated uncertain overall in the setting of mild-to moderate CD, while MTX was rated as the third-line appropriate therapy, but only after both IFX and steroid failure and/or loss of response. Natalizumab was considered inappropriate in all situations (Fig. 1).

3.2. Severe active luminal Crohn's disease

The panel rated high, moderate and severe CD together. In this setting, high-dose steroids (defined as 1–1.5 mg/kg body weight per day p.o. or i.v.) remained the first option.

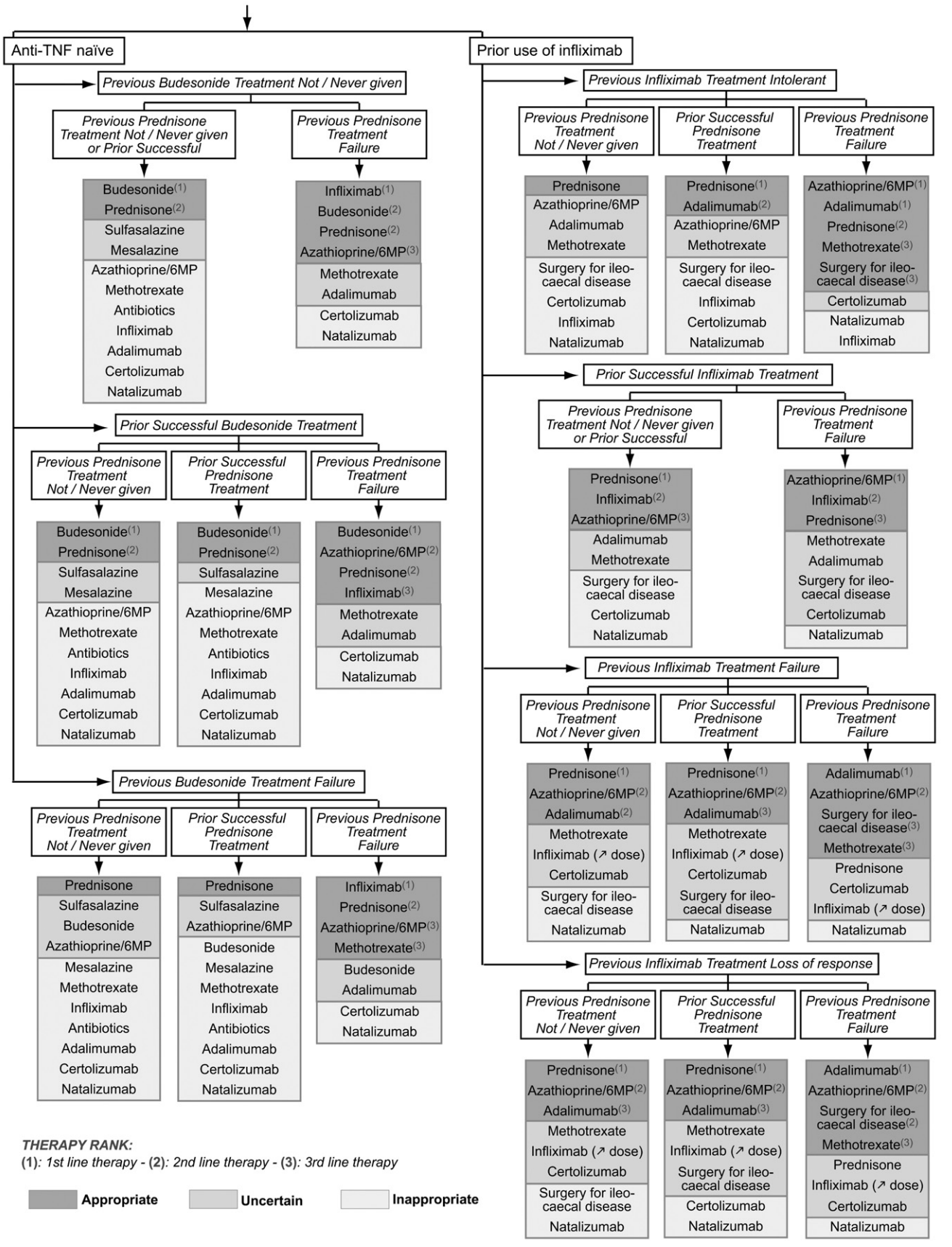

Figure 1 Appropriateness ratings of therapy for mild to low-moderate CD.

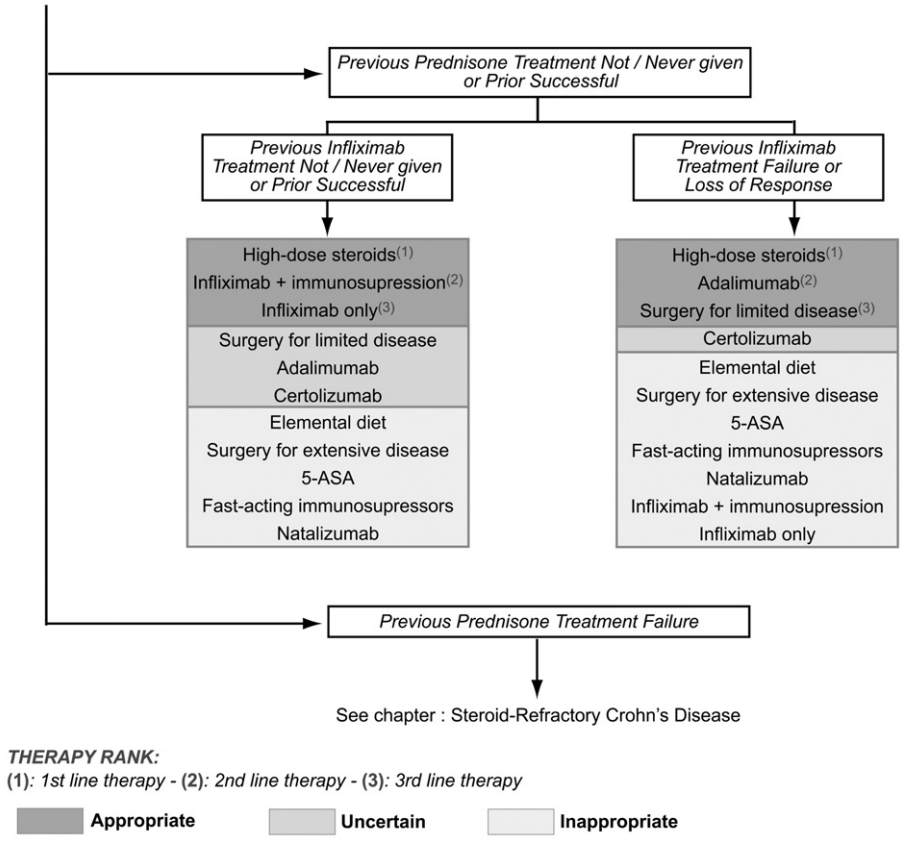

Figure 2 Appropriateness ratings of therapy for high moderate-to-severe CD.

IFX with or without co-administration of immunosuppression were rated appropriate. After prior failure of IFX, adalimumab as well as surgery (for limited disease) were deemed appropriate. There was uncertainty concerning the use of certolizumab pegol in this group of patients. All other approaches, including 5-ASA, elemental or polymeric diet, fast-acting immunosuppressors, natalizumab and surgery for extensive disease, were considered inappropriate (Fig. 2).

3.3. Steroid-dependent Crohn's disease

AZA-6MP was considered as the first option to be tested in ST-D patients and MTX the second option. IFX with an immunosuppressor was rated as an alternative option to both immunomudulators given alone. There was uncertainty regarding the use of IFX alone, adalimumab and surgery in AZA/6MP naïve patients. When AZA/6MP and MTX have failed, IFX, adalimumab and surgery for limited disease were rated appropriate. Certolizumab pegol was considered uncertain after AZA/6MP failure. Natalizumab and surgery for extensive resection were rated inappropriate (Fig. 3).

3.4. Steroid-refractory Crohn's disease (Fig. 3)

AZA/6MP, MTX, IFX with immunosuppression, adalimumab and surgery for limited resection were all considered appropriate after previously successful AZA/6MP therapy or in naïve patients. The ranking further indicates that the panel rated at least one immunosuppressor prior to the use of biologics in this setting. There was disagreement on the use of infliximab alone and of certolizumab pegol, which were both rated uncertain. After AZA/6MP and MTX failure, infliximab alone was considered appropriate as a first-line drug. Surgery for limited disease and adalimumab were appropriate as second-and third-line therapy respectively. Elemental or polymeric diet, natalizumab and surgery for extensive disease were judged inappropriate for all indications.

4. Discussion

The process of applying high-quality evidence from randomized trials or even from meta-analyses to clinical decisions leaves many situations unresolved. The development of explicit criteria, based on precise clinical scenarios, to define the appropriateness of care thus fills a significant gap between the evidence in the literature and the bedside, with the aim of improving quality of care. In addition, such criteria are highly relevant as instruments for outcome research, in particular for the analysis of large patient databases such those currently being assembled in several countries and through international IBD consortia. Finally, such criteria may help define precise patient phenotypes in terms of treatment response, an important step in pharmacogenetic and pharmacogenomic analyses. The validated and respected RAND Appropriateness Method,[45] used during the two EPACT panels, is well suited to define treatment

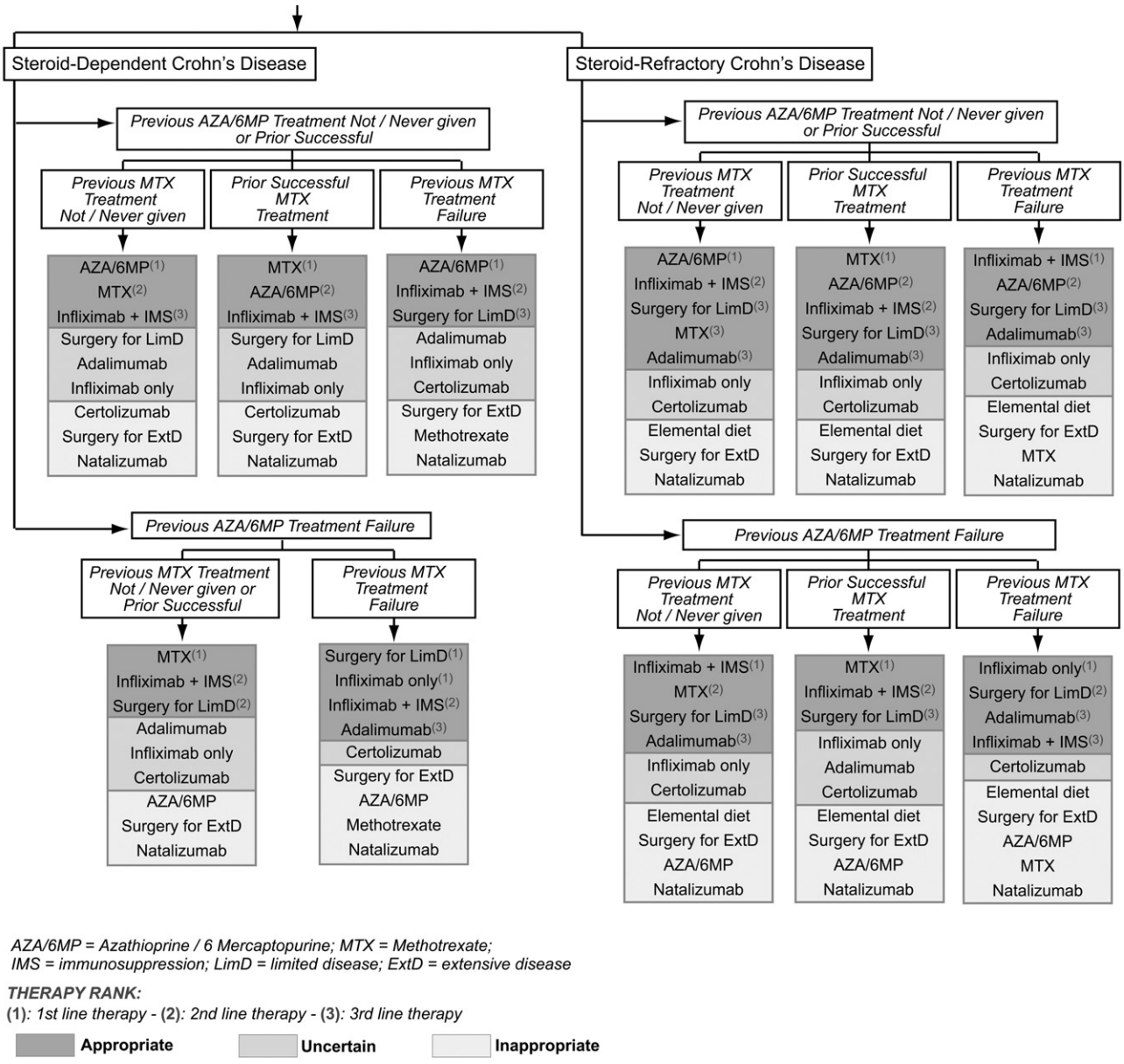

Figure 3 Appropriateness ratings of therapy for steroid-dependant or-refractory CD.

criteria for all the many situations met by clinicians in the care of CD patients.

With respect to active luminal (non-penetrating, non-fistulizing) CD, the option chosen by the EPACT II panel was to stratify the possible scenarios based on the usual broad patient categories of mild-to-low-moderate, high-moderate-to-severe, steroid-dependent and steroid-refractory disease, as these broad categories correspond to readily-identifiable clinical situations as well as to stratifications frequently used as inclusion or analysis criteria in clinical trials. There is some overlap in the moderate active CD category, reflecting the relatively broad range of patient disease scores in studies, which in turn reflects the polymorphism of the disease and the lack of precision of the commonly used disease scores. Clinicians, however, generally accept these categories.

The ratings established during EPACT II for mild-to-low-moderate active CD (Fig. 1), confirmed the role of budesonide in this group of patients. The efficacy of this drug has recently been confirmed by a Cochrane collaboration review.[49] The EPACT panel, however, did not identify any situations in which 5-ASA compounds or salazopyrine would be indicated in this group of patients. These conclusions concur with the ECCO guidelines for the treatment of Crohn's disease.[50] Biologics were not deemed appropriate in this milder form of the disease, unless steroids, including not only budesonide but also systemic steroids, had failed. This position recognizes that systemic steroids, although similar in efficacy to budesonide in clinical trials, are probably still efficacious when budesonide fails, especially in the sicker patient segment of this category. The steroid-based approach to this group of patients leaves biologics, and in particular anti-TNF agents, as second-line therapies, which may be seen as a conservative approach. The panel discussed this point with the definition of appropriateness in mind, which demands that the benefit of any therapy for the

patient outweigh its risks. In patients likely to respond well to a course of steroids, appropriateness of steroids is good, in particular budesonide. This definition does not incorporate maintenance therapy, however, which should in practice be considered in the global view of a patient's therapeutic plan.

In moderate-to severe CD patients, AZA/6-MP rated better than IFX. The recently presented SONIC trial,[51] although not yet available as a full publication, reports on the first direct comparison of AZA to IFX and reported better results with IFX or IFX and AZA than with AZA alone. The patients included in this study had to be naïve to AZA, but not to steroids, with a CDAI typical of active disease. Thus 41% of the SONIC patients were in fact steroid-refractory, and for this reason not directly similar to the EPACT scenario discussed here and not thus not directly comparable to the classic Candy et al study, in which steroids were used as a bridge therapy with AZA.[52] The SONIC results nevertheless suggest that an earlier use of IFX than previously recommended. Sub-analyses of this important trial will help define the patient subgroups best suited to early combination therapy with IFX and AZA. In patients in whom systemic steroids had failed, the panel also recommended infliximab as an appropriate therapy, which is perfectly in line with the situation of 41% of SONIC patients. In this situation, the other anti-TNF agents are probably also indicated, but data regarding these agents were less abundant and these drugs not yet commercially available at the time of the conference. As the definition of appropriateness used recognizes a benefit-to-risk ratio, the size of the safety database for each compound also counts in the rating.

The EPACT II panel elected to rate patients with prior IFX exposure as a separate group among patients with moderate-to-severe CD, as clinical decisions may differ in this group of patients whose response to an anti-TNF agent is known. If the use of IFX had previously been successful, this drug was deemed appropriate, as well as systemic steroids, but not budesonide, as the panel accepted the principle that such patients have a disease probably too severe to warrant a test with this compound. AZA could also be used in these patients. When a patient had previously been intolerant of IFX, the panel recommended either prednisone or adalimumab. The panel still preferred the use of steroids, if those had never been used or were previously successful. In the opposite eventuality, then both classes of immunomudulators were proposed, as well as surgery if the disease was located in the ileo-caecal region. The inclusion of surgery at this stage took into account the potential toxicity of accumulated immunosuppressive agents. The same approaches prevailed, with minor differences that are illustrated in Fig. 1, for patients with primary IFX failure. The situation differed, however, in patients with secondary failure of IFX, the well-known loss-of-response situation. In this group of patients, the panel included a switch to adalimumab in the first choices, even rating it first in patients with prior steroid failure (failure includes intolerance as defined by the panel). The panel did not rate an escalation of the IFX dose as appropriate. This decision may be debatable, as evidence exists for each anti-TNF agent that shows that dose escalation is safe and effective in restoring response in patients with loss of response.[18,41,53] Certoluzimab pegol has also shown effectiveness in patients with prior IFX exposure,[53] and should have been included in the possible choices here. Once again, the lack of a large safety database counted against this medication in the ratings.

Steroid-dependent and refractory patients were rated separately, to reflect the specific clinical challenges posed by these patients. In these patients, the classical approach of using immunosuppressors (AZA and then MTX if the latter fails) prevailed in the decisions of the EPACT II panel. Anti-TNF agents, and in particular IFX, were only rated as appropriate after prior failure of AZA and MTX. Again, IFX rated above the other anti-TNF agents. The panel here accepted the view that on average IFX has a faster onset of action, which is favorable in these groups of sick patients. IFX was always recommended concomitantly with the use of immunosuppressors, which would probably already be part of the prescription at this stage. The panel again rated the appropriateness of surgical resection in these patients relatively highly, in those with limited disease extension, to underline the importance of avoiding multiple drug exposure and prolonged active disease courses in these patients.

An approach such as the RAM, as used by the EPACT II panel, has of course some limitations. Among them, one such limitation being the number of given situations that can be taken into account, because each new parameter implies further additional scenarios, on which the panelists will have to cast a vote. As the whole process is deemed to be driven by evidence where available, data from studies should support most decisions. With this in mind, the EPACT panel decided not to include potential prognostic indicators (e.g. young age, steroids at first presentation, fistulas, etc) as potential modifiers of the scenarios. This aspect should remain in the hands of the physician using these criteria.

A top-down approach to Crohn's disease management has recently been proposed after a successful demonstration in a randomized trial.[54] The construction of the scenarios used during EPACT II is not suited to addressing whether a step-up or a top-down approach would be preferable in each clinical situation. We cannot thus perform even an exploratory post hoc analysis of the panel votes to evaluate the potential impact of the introduction of this parameter in the decision trees. Although the top-down approach is promising for improving long-term disease outcome, it carries the intrinsic risk of over-treating a substantial number of patients. Such over-treatments, with their associated side-effects, may substantially alter the benefit-risk ratio of the top-down therapy for a number of patients. At the present time, there is insufficient data to determine the appropriateness of care of such approach, if appropriateness is defined as the optimal benefit-risk ratio for the patient considered for a given therapy.

In conclusion, the criteria used by the EPACT II panel allowed a representative group of experts to rate the appropriateness of the various therapeutic options available for the management of active luminal CD. These criteria may help the clinician to make decisions in everyday practice. These criteria are available in an interactive form on an open-access website (www.epact.ch). The ratings of the panel were largely based on the available literature but, interestingly, also reflected some gaps between "know" and "do" as well as some fears about the long-term safety of recently introduced agents. One of the originalities of this second EPACT conference was to provide an order of preference among the drugs deemed appropriate in each

situation where more than one choice existed. This feature of the ratings was designed to further help the clinician to make the best possible clinical decision, which should remain based on the clinical assessment of each individual patient.

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References

1. Cohen RD. The quality of life in patients with Crohn's disease. *Aliment Pharmacol Ther* 2002;**16**(9):1603–9.
2. Hanauer SB, Sandborn W. Management of Crohn's disease in adults. *Am J Gastroenterol* 2001;**96**(3):635–43.
3. Summers RW, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;**77**(4 Pt 2):847–69.
4. Malchow H, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;**86**(2):249–66.
5. Hanauer SB, Stromberg U. Efficacy of oral Pentasa (R) 4 g/day in treatment of active Crohn's disease: a meta-analysis double-blind, placebo-controlled trials. *Gastroenterology* 2001;**120**(5):2308.
6. Campieri M, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997;**41**(2):209–14.
7. Rutgeerts P, et al. A comparison of budesonide with prednisolone for active Crohn's disease. *N Engl J Med* 1994;**331**(13):842–5.
8. Kane SV, et al. The effectiveness of budesonide therapy for Crohn's disease. *Aliment Pharmacol Ther* 2002;**16**(8):1509–17.
9. Faubion Jr WA, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001;**121**(2):255–60.
10. Munkholm P, et al. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut* 1994;**35**(3):360–2.
11. van Dullemen HM, et al. Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology* 1995;**109**(1):129–35.
12. Cohen RD, Tsang JF, Hanauer SB. Infliximab in Crohn's disease: first anniversary clinical experience. *Am J Gastroenterol* 2000;**95**(12):3469–77.
13. Farrell RJ, et al. Clinical experience with infliximab therapy in 100 patients with Crohn's disease.[comment]. *Am J Gastroenterol* 2000;**95**(12):3490–7.
14. Hanauer SB, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**(9317):1541–99.
15. Sandborn WJ, et al. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. *Am J Gastroenterol* 2004;**99**:1984–9.
16. Papadakis KA, et al. Safety and efficacy of adalimumab (D2E7) in Crohn's disease patients with an attenuated response to infliximab. *Am J Gastroenterol* 2005;**100**(1):75–9.
17. Hinojosa J, et al. Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: a prospective, open-label, multicentre trial. *Aliment Pharmacol Ther* 2007;**25**(4):409–18.
18. Colombel JF, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**(1):52–65.
19. Sandborn WJ, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;**146**(12):829–38.
20. Winter TA, et al. Intravenous CDP870, a PEGylated Fab' fragment of a humanized antitumour necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. *Aliment Pharmacol Ther* 2004;**20**(11–12):1337–46.
21. Schreiber S, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 2005;**129**(3):807–18.
22. Sandborn WJ, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007;**357**(3):228–38.
23. Colombel J, et al. Certoluzimab pegol administered subcutaneously is effective in anti-TNF naive patients and in patients previously treated with infliximab. *Gut* 2006;**55**(suppl):A21.
24. Macdonald J, McDonald J. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;**1**:CD006097.
25. Fernandez-Banares F, et al. How effective is enteral nutrition in inducing clinical remission in active Crohn's disease? A meta-analysis of the randomized clinical trials. *JPEN J Parenter Enteral Nutr* 1995;**19**(5):356–64.
26. Griffiths AM, et al. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. *Gastroenterology* 1995;**108**(4):1056–67.
27. Messori A, et al. Defined-formula diets versus steroids in the treatment of active Crohn's disease: a meta-analysis. *Scand J Gastroenterol* 1996;**31**(3):267–72.
28. Candy S, et al. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995;**37**(5):674–8.
29. Ewe K, et al. Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. [comment]. *Gastroenterology* 1993;**105**(2):367–72.
30. Present DH, et al. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980;**302**(18):981–7.
31. Rhodes J, et al. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;**2**(7737):1273–6.
32. Willoughby JM, et al. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;**2**(7731):944–7.
33. Klein M, et al. Treatment of Crohn's disease with azathioprine: a controlled evaluation. *Gastroenterology* 1974;**66**(5):916–22.
34. Pearson DC, et al. Azathioprine and 6-Mercaptopurine in Crohn Disease—a metaanalysis. *Ann Intern Med* 1995;**123**(2):132–42.
35. Oren R, et al. Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997;**92**(12):2203–9.
36. Arora S, et al. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999;**46**(27):1724–9.
37. Feagan BG, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. [comment]. *N Engl J Med* 1995;**332**(5):292–7.
38. Cohen RD. Efficacy and safety of repeated infliximab infusions for Crohn's disease: 1-year clinical experience. *Inflamm Bowel Dis* 2001;**7**(Suppl 1):S17–22.
39. Hommes DW, et al. Infliximab treatment for Crohn's disease: one-year experience in a Dutch academic hospital. *Inflamm Bowel Dis* 2002;**8**(2):81–6.
40. Ricart E, et al. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. *Am J Gastroenterol* 2001;**96**(3):722–9.

41. Rutgeerts P, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;**126**(2):402–13.
42. Panis Y. Surgical management of patients with inflammatory bowel disease: consensus and controverse. *Gastroenterol Clin Biol* 2003;**27**(3 Suppl):S92–7.
43. Michetti P, et al. Therapy of mild to moderate luminal Crohn's disease. *Digestion* 2005;**71**(1):13–8.
44. Michetti P, et al. Severe and steroid-resistant Crohn's disease. *Digestion* 2005;**71**(1):19–25.
45. Naylor CD. What is appropriate care? *N Engl J Med* 1998;**338**(26):1918–20.
46. Vader JP, et al. Appropriate treatment for Crohn's disease: methodology and summary results of a multidisciplinary international expert panel approach-EPACT. *Digestion* 2006;**73**(4):237–48.
47. Juillerat P, et al. EPACT II: project and methods. *Digestion* 2007;**76**(2):84–91.
48. Brook RH, et al. A method for the detailed assessment of the appropriateness of medical technologies. *Int J Technol Assess Health Care* 1986;**2**(1):53–63.
49. Benchimol EI, et al. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009(1):CD002913.
50. Travis SP, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006;**55**(Suppl 1):i16–35.
51. Colombel J, et al. Sonic: a randomized, double-blind, controlled trial comparing infliximab and infliximab plus azathiprine to azathioprine to patients with Crohn's disease naive to immunomodulators and biologic therapy. *Gut* 2008;**57**(suppl II):A1 (abstract no OP0001).
52. Candy S, et al. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995;**37**(5):674–8.
53. Schreiber S, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;**357**(3):239–50.
54. D'Haens G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;**371**(9613):660–7.