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SPECIAL ARTICLE

Physician perspectives on unresolved issues in the use of conventional therapy in Crohn's disease: Results from an international survey and discussion programme

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Abstract

Background and aims: Data on the optimal use of conventional therapies in Crohn's disease are lacking in guidelines. An educational programme was established to explore questions raised in clinical practice and to provide practical answers.

Abbreviations 6-MP, 6-mercaptopurine; BMD, bone mineral density; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ECCO, European Crohn's and Colitis Organisation; HSTCL, hepatosplenic T cell lymphoma; IBD, inflammatory bowel disease; ISC, International Steering Committee; TNF, tumour necrosis factor; TPMT, thiopurine methyltransferase.

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Methods: Telephone interviews with 96 gastroenterologists and a web survey of 1370 gastroenterologists identified 26 key questions. Ten questions were taken forward to the next stage based on the opinion of an International Steering Committee. Draft answers to the questions were prepared from available evidence following a literature search. The draft answers were debated in national meetings of participating countries (n = 36) and voted on using a standard scoring system. Revised answers went forward to an international meeting and were debated and voted on using the same methodology. Final answers were developed, based on evidence and clinical experience of the participants.

Results: Evidence on corticosteroid and immunomodulator use such as dosage, timing and duration, choice of drug or regimen, and safety is scarce. Key points of the answers included the importance of: identifying patients with poor prognosis; early intervention with optimal doses of immunomodulators; avoiding prolonged or repetitive corticosteroid therapy; achieving corticosteroid-free remission; achieving a balance between clinical benefit and safety when intensifying or prolonging therapy or combining different agents; re-evaluating therapy at appropriate time points; and considering the role of biomarkers and mucosal healing.

Conclusions: The answers to 10 key questions were based on available evidence and clinical experience of programme participants. It is hoped they will be of practical use in everyday gastroenterology practice.

1. Introduction

Crohn's disease is a chronic inflammatory bowel disorder characterised by alternating periods of clinical remission and relapse. Current management focuses on inducing and maintaining clinical remission, and recent guidelines are available from the European Crohn's and Colitis Organisation (ECCO)[1,2] and the American College of Gastroenterology.[3] Corticosteroids and immunomodulators have been used for decades in inflammatory bowel disease (IBD), including Crohn's disease,[4–6] and are recommended by the guidelines across the spectrum of disease severity, while anti-tumour necrosis factor (TNF) agents were introduced in the late 1990s.

High-quality data from controlled clinical trials are limited for corticosteroids and immunomodulators. Indeed, both European and US guidelines acknowledge that many questions regarding best practice in the management of Crohn's disease remain unanswered because of insufficient data, and that treatment is often a matter of judgement and best practice.[2,3] Thus, guidelines give relatively little direction on the precise use of corticosteroids and immunomodulators in terms of dosage, mode of administration and duration of therapy. As a result of such uncertainties in the guidelines, it therefore seems highly likely that physicians involved in the day-to-day management of Crohn's disease will have many questions about the best use of these conventional therapies in their clinical practice.

An educational programme, 'IBD Ahead 2010', was established to explore questions commonly raised by clinicians about the optimal use of corticosteroids and immunomodulators in the management of Crohn's disease. Gastroenterologists from many countries worldwide were actively involved in the programme through market research activities and discussions at national and international meetings. The goal of the programme was to provide practical answers to questions raised in everyday clinical practice, based on available evidence and the clinical experience of programme participants.

2. Methods

A total of 36 countries worldwide participated in the programme. It was overseen by an International Steering Committee (ISC) made up of 16 gastroenterology specialists from Europe, Canada, Australia, Turkey and Japan (members are listed in Acknowledgements). In addition, each participating country had its own National Steering Committee. The ISC was chaired by two of the authors of the present paper (J-FC and RP).

The programme took place between July 2009 and December 2010 and consisted of several stages (Fig. 1). Telephone interviews were initially conducted with 96 gastroenterologists from nine countries (Belgium, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, UK) to identify key unanswered questions in the routine use of corticosteroids and immunomodulators in the treatment of Crohn's disease. A total of 26 questions were identified and fed into a web-based survey of 1370 gastroenterologists who ranked the importance of each question. The results from the web-based ranking were debated at a meeting of the ISC held in November 2009, and agreement on which questions the ISC considered to be the most important was obtained via informal debate. In some cases, two or more of the 26 questions were combined and a total of 10 questions went forward to the next stage.

Draft answers to the 10 questions were prepared by authors of the present paper. PubMed and Embase were searched using pre-defined search strings and limits, and additional searches were conducted by hand as required. Abstracts from the following conferences were searched: American College of Gastroenterology, ECCO, Digestive Disease Week and United European Gastroenterology Week. No time limits were included in the search criteria except for conference abstracts, which were limited to 2007–2009. National meetings were held to present the draft answers to the National Steering Committee of 35 out of the 36 participating countries and other nationally-recognised gastroenterologists. Participants voted on their level of

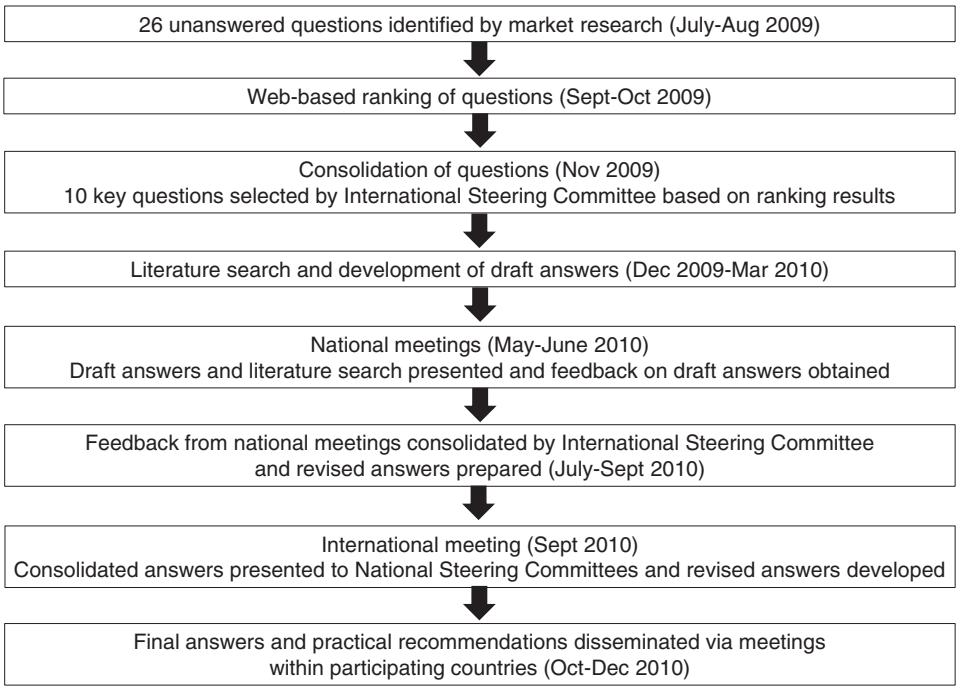

Figure 1 Overview of the programme.

agreement with each draft answer using a scale of 1 to 9 (where 1 = strong disagreement and 9 = strong agreement). Each voting score was allocated to one of three ranges: 1–3, 4–6 and 7–9. If ≥75% of participants scored within the 7–9 range, then the answer was deemed to be agreed upon. If <75% of participants scored within this range, the answer was debated and revised, and a second vote took place. Again, if ≥75% of participants scored within the 7–9 range, the answer was deemed to be agreed upon. If agreement was not reached at this stage, a lack of agreement was noted. Similar methodology has been employed in development of consensus-based guidelines in the UK.[7,8] Feedback from each country was consolidated into revised answers, taking into account consistency between countries and alternative views.

The revised answers were discussed and voted upon at an international meeting attended by participants from 30 out of the 36 participating countries; each country had one vote per question. In each vote, the countries indicated their level of support for the revised answer using the same voting methodology as in the national meetings. This was not a formal consensus or Delphi process; the voting aimed to achieve answers on which all participants had reached broad agreement. Notable differences between countries were discussed at the international meeting. As in the national meetings, agreement on the answer was defined as ≥75% of participants scoring the answer within the 7–9 range on the scale.

3. Results and discussion

The results of the web-based survey are shown in Supplementary Table 1. The questions and final answers agreed upon after voting at the international meeting are described below. Agreement on answers was achieved for all 10 questions.

Question 1: Introduction of corticosteroids

1. When should we introduce corticosteroids, and for how long?
   1. Systemic corticosteroids are best used for moderately to severely active Crohn's disease of any location. Their use in isolated perianal Crohn's disease is not supported.
   2. Budesonide is preferred to systemic corticosteroids for mildly to moderately active ileocaecal disease and right colonic disease, but is not universally available. In countries where budesonide is not available, early introduction of immunomodulators (and/or anti-TNF therapy) for their corticosteroid-sparing properties is appropriate.
   3. The duration of initial treatment with systemic corticosteroids at full dose depends on the response of the patient. There is no clear evidence that continuing the full dose (40–60 mg prednisone or equivalent) beyond weeks 1–3 influences remission rates. Patients who do not respond within 2–4 weeks had best be further investigated and other therapeutic options considered.

   100% agreement after 2nd vote

The effect of systemic corticosteroids on remission induction in Crohn's disease has been studied in several uncontrolled and controlled trials. In a Cochrane systematic review of controlled trials, systemic corticosteroids were significantly more effective than placebo and 5-aminosalicylic acid (mesalamine, mesalazine).[9] The clinical response rate achieved in the studies varied from 60% to 97% over 1–5 months in mildly to severely active disease of any location. However, in fistulising perianal Crohn's disease, corticosteroids are ineffective[10] and therefore their use in perianal

disease is only justified to treat concomitant luminal disease.

Another Cochrane review has shown that budesonide is significantly more effective than placebo or mesalamine in short-term remission induction (within 8 weeks of treatment) in moderately active Crohn's disease, but is less effective than systemic corticosteroids in severe disease (characterised as Crohn's Disease Activity Index [CDAI] >300).[11] A recent randomised, double-blind, multicentre trial has demonstrated equal efficacy of budesonide and mesalamine, for induction of remission in mildly to moderately active right-sided colonic Crohn's disease.[12] If the results are confirmed in other studies, mesalamine may be an alternative to budesonide in these patients. With regard to its pharmacokinetic characteristics, it is important to emphasise that budesonide is only effective in Crohn's disease located in the terminal ileum and/or proximal colon.[13]

The suggestion of an early introduction of immunomodulators and/or anti-TNF agents where budesonide is unavailable is based on opinion, as no data are currently available on the risk–benefit ratio of this approach. A multicentre, randomised, open-label study comparing conventional treatment (systemic corticosteroids followed by immunomodulators in the case of relapse after corticosteroid-tapering) versus early combined immunosuppression (three infusions of infliximab and concomitant immunomodulators) showed no difference in the corticosteroid-free remission rate between the two groups beyond 1 year.[14] However, it is difficult to extrapolate these data to budesonide, as patients who are candidates for budesonide therapy may have different characteristics to those receiving systemic corticosteroids. Factors other than local availability of budesonide (i.e. age, gender, disease phenotype and behaviour, possibility of limited surgery) should be considered in the decision to introduce immunomodulators and/or anti-TNFs as an alternative to budesonide.

For remission induction in active Crohn's disease, most studies of systemic corticosteroids have used a full dose (40–60 mg prednisolone equivalent) for 1–3 weeks, followed by different tapering regimens. Although one study from the GETAID group showed a maximal clinical response rate at week 7,[15] the 18-month remission rate in the follow-up study was only 34%.[16] Thus, as the risk of side effects increases with cumulative doses of corticosteroids, continuing these drugs at full dose beyond 1–3 weeks does not appear to be justified.

Question 2: Dosing strategy for corticosteroids

2. What is the best dosing strategy for the use of corticosteroids, in terms of: starting and maximum doses, duration, dose escalation/de-escalation (when? rate?), formulation, avoiding side effects? What duration of corticosteroid treatment is linked to the occurrence of side effects?
1. The optimal initial dose of oral systemic corticosteroids in Crohn's disease ranges from 40 to 60 mg/day to 1 mg/kg/day. For intravenous hydrocortisone, the optimal starting dose is 300–400 mg/day.
2. The optimal starting dose of budesonide is 9 mg/day.
3. Tapering of corticosteroids is generally initiated within a week of starting therapy, and after no more than 3–4 weeks. There are no trials assessing different tapering regimens, and 'standard' regimens differ amongst centres. A reasonable approach is to reduce the dose by 5 mg/week, tapering to zero over 8 weeks (from an initial dose of 40 mg/day). Treatment should not exceed 12 weeks except in exceptional circumstances. Early introduction of immunomodulators or anti-TNF therapy is appropriate.
4. No data are available to allow evaluation of any benefit of intentional dose escalation of corticosteroids.
5. Systemic corticosteroids and budesonide are ineffective as maintenance therapy. It is strongly recommended to taper all corticosteroids to zero and switch appropriate patients to immunomodulator (or anti-TNF) therapy.
6. Corticosteroids have been shown to increase the risk of serious, opportunistic infections and mortality, both independently or in combination with immunomodulators and anti-TNF agents.
7. The best way to prevent corticosteroid-induced side effects is to avoid prolonged or repetitive use and to switch appropriate patients to immunomodulator therapy and/or anti-TNF therapy. Surgery is an appropriate option for some patients demonstrating corticosteroid dependency and could be considered.
8. To prevent corticosteroid-induced loss of bone mineral density, calcium and vitamin D supplements should be provided. Clinicians treating with corticosteroids should familiarise themselves with local guidelines in managing corticosteroid-induced metabolic bone disease.
9. Not all corticosteroid-induced side effects occur dose- or time-dependently.
94% agreement after 2nd vote

No formal dose–response trials have been performed with systemic corticosteroids in Crohn's disease. The usual starting dose for induction of remission in active Crohn's disease is 40–60 mg prednisolone or equivalent. A higher starting dose of 1 mg/kg seems to increase the short-term remission rate (reviewed by Lichtenstein et al.[17]); however, no comparative studies have been performed. For budesonide, a landmark placebo-controlled, randomised, double-blind trial in active ileal or proximal colonic disease showed the highest remission rate (51%) at 8 weeks with a dose of 9 mg compared with doses of 3 and 15 mg.[18]

Only one study provides a head-to-head comparison of two different systemic corticosteroid tapering regimens on short- and medium-term (6 months) remission rates, showing no difference between a 4-week versus a 12-week tapering regimen.[19] In addition, none of the various tapering regimens used across different studies have resulted in more favourable long-term outcomes. In general, the evidence on dosing and tapering of corticosteroids is limited. Therefore, the proposed tapering regimen and maximum treatment duration of approximately 12 weeks for systemic corticosteroids should be seen as opinion which achieves a compromise between the maximum benefit on remission rate and the risk of cumulative dose-related side effects. For budesonide, the best efficacy in remission induction has been achieved with a full 9 mg dose used over 8 weeks,[18] with tapering thereafter.

No data are available on the utility of intentional dose escalation of corticosteroids when remission has not been achieved. Regarding maintenance of remission, two

Cochrane reviews have concluded that systemic corticosteroids and budesonide are ineffective in this setting.[20,21]

It has been demonstrated that the use of corticosteroids carries the risk of opportunistic infections[22] and the risk appears to increase with dose and prolonged treatment.[23] Early introduction of immunomodulators and/or anti-TNF agents seems to be a reasonable approach to limit these complications by facilitating corticosteroid withdrawal. However, there is also a risk of infectious complications with immunomodulators and anti-TNF agents, which is increased with use of multiple agents. Therefore, surgery may be considered in patients in whom it is not possible to withdraw corticosteroids in spite of immunomodulator and/or anti-TNF therapy.

The key to prevention of corticosteroid-induced loss of bone mineral density (BMD) is limitation of the cumulative dose of corticosteroids. No extensive evidence of any benefit of vitamin D and calcium supplementation on BMD is available for patients with Crohn's disease receiving corticosteroids. Nevertheless, the recommendation of standard supplementation of vitamin D and calcium is supported by data in the healthy elderly showing a reduction of the risk of fractures with this approach, together with demonstrated vitamin D deficiency in Crohn's disease patients.[24]

Corticosteroid-related side effects can occur at any time during treatment.[1] Neuropsychiatric side effects, hypertension, cosmetic side effects (moon face, acne, hirsutism) as well as pituitary axis suppression may occur as soon as within 2 weeks of starting therapy. Loss of BMD depends on the cumulative dose of corticosteroids but may be manifested by fractures as early as within 2 months of treatment. It is not clear what duration of treatment is related to the development of cataracts but seems to be at least 1 year in adults.

Question 3: Introduction of immunomodulators

3. How early should immunomodulators be introduced and which regimen should be used?
   1. Initiation of immunomodulators (±anti-TNF therapy) early in the disease course (often within a week or two of diagnosis) should be considered for patients with severe disease, paediatric patients and for patients at high risk of progression to disabling disease.
   2. It is generally appropriate to start thiopurines or methotrexate in immunomodulator-naïve patients who have a relapse, are corticosteroid-dependent, or who need repeated courses of corticosteroids. This may include patients who need two or more courses of corticosteroids within 12 months; who relapse as the corticosteroid dose is tapered below 15 mg; or who relapse within 3 months of stopping corticosteroids. These limits are arbitrary, but serve as guidance for clinical practice. The aim is to withdraw corticosteroids completely.
   3. Thiopurines are currently indicated for postoperative prophylaxis immediately after surgical resection of ileocolonic disease. This is true in patients with high risk of recurrence; in the other patients thiopurines should be introduced if there is evidence of recurrence at 6–12 months.
   89% agreement after 2nd vote

Crohn's disease exhibits a wide phenotypic spectrum at diagnosis, and becomes more disabling over time in a considerable proportion of patients, either through development of complications such as abscesses, internal fistulae and strictures, or as a result of cumulative structural damage.[25] Initiation of immunomodulators early in the disease course—namely close to diagnosis—in patients already demonstrating or at risk of complicated disease seems reasonable since it may induce long-term corticosteroid-free remission.[5] Specifically, the goal should be induction of mucosal healing and achievement of a symptom-free everyday life, with minimal use of corticosteroids.[14,26,27] Children seem to benefit more from early initiation of immunomodulators; indeed, children treated early with 6-mercaptopurine (6-MP) showed a superior outcome compared with those receiving placebo.[28] However, recent data do not support any advantage of early initiation of azathioprine to induce long-term corticosteroid-free remission in recently diagnosed adult Crohn's disease.[29]

Clinical variables associated with a complicated disease course (defined in most studies as the need for resection, progression towards stricturing or penetrating behaviour or development of steroid dependency) include active smoking, age less than 40 years, extensive length of affected digestive tract, perianal lesions, extraintestinal manifestations, corticosteroid therapy during the first flare and perhaps persistently elevated C-reactive protein (CRP). Such variables have been proposed as predictors of a worse prognosis in medically treated patients with Crohn's disease.[30] Although these variables have not been validated in adequately powered prospective clinical trials, they do identify patients who would benefit most from early aggressive therapy. ECCO guidelines propose a series of (in certain cases, arbitrary) definitions to serve as a guide for therapy decision-making: corticosteroid-refractory and -dependent patients are indicated as the best candidates for early treatment intensification.[2]

Most complications of Crohn's disease need surgical interventions that lead to more disabling disease. However, surgery does not provide a cure, since the disease almost invariably recurs close to the anastomosis. Postoperative recurrence following ileocaecal resection for therapy-resistant ileocolitis in Crohn's disease predominately occurs in the pre-anastomotic area in the neoterminal ileum and progresses in a few years from aphthae to larger ulcers and stricture; however, clinical symptoms can appear 2–3 years after the development of early mucosal lesions.[31] Azathioprine either as monotherapy or combined with a baseline course of metronidazole is the agent of choice to prevent recurrence in the postoperative setting based on prospective evidence.[32–34] However, azathioprine appears to be less effective in patients with severe endoscopic recurrence.[35] Smoking, prior intestinal resection (including appendectomy), penetrating disease behaviour prior to surgery, perianal location and extensive small bowel resection have been shown to predict early postoperative recurrence and thus mandate an aggressive therapeutic approach immediately after surgery. Low risk patients can be offered an endoscopy at 6–12 months after surgery and treated according to endoscopic findings and clinical status.[36,37]

Nonetheless, the potential benefit of early initiation of immunomodulators must be weighed against the possibility of an increased risk of treatment-emergent side effects such as more frequent infections or a higher rate of malignancies.

Question 4: Dosing strategy for immunomodulators

4. What is the best dosing strategy for immunomodulators, in terms of: starting and maximum doses, duration, dose escalation/de-escalation (when? rate?), which immunomodulator first?
1. The most effective doses appear to be 2.0–3.0 mg/kg/day for azathioprine and 1.0–1.5 mg/kg/day for mercaptopurine. Initial dose strategies in common practice are either a gradual dose increase starting with 50 mg parenteral azathioprine (25 mg mercaptopurine) or full dose therapy with prior determination of thiopurine methyltransferase (TPMT) activity/genotype.
2. For methotrexate, the dosing strategy best supported by evidence from clinical trials is 25 mg per week for 8–12 weeks and 15 mg per week for maintenance.
3. Azathioprine is generally used as a first-line immunomodulator.
4. Azathioprine/mercaptopurine treatment is best maintained for several years because of the high relapse rates in patients with Crohn's disease when these drugs are discontinued.
93% agreement after 2nd vote

Both thiopurine drugs, azathioprine and 6-MP, are effective, corticosteroid-sparing immunomodulators for the induction (although their onset of action is slow) and maintenance of pre- and postoperative remission in luminal Crohn's disease. The most effective doses appear to be 2.0–3.0 mg/kg for azathioprine and 1.0–1.5 mg/kg for 6-MP when administered orally. A trial evaluating whether the onset of action could be accelerated found that a high dose infusion given over 36 h was no more effective than conventional oral dosing.[38] Higher response rates have been obtained with azathioprine than with 6-MP, and thus azathioprine is generally preferred as a first-line immunomodulator therapy,[39-41] although the only randomised controlled trial evaluating 6-MP used a low dose.[33] Future studies should evaluate higher doses.

It has not yet been well determined how best to start therapy: dose escalation to the weight-based dose versus starting immediately at the weight-based dose (no randomised controlled trials comparing the two strategies have been conducted). There is more tertiary-centre evidence to support the dose escalation method: azathioprine may be started at 50 mg daily and the dose increased by 25 mg every 1–2 weeks to a target dose of 2.0–3.0 mg/kg/day along with monitoring for leukopenia and other potential adverse events. 6-MP may be started at 25 mg daily and the dose increased by 25 mg every 1–2 weeks to a dose of 1.0–1.5 mg/kg/day, also with monitoring.[40] Azathioprine and 6-MP are prodrugs that undergo extensive metabolism. TMPT has a major role in this metabolism. Measurement of azathioprine and 6-MP metabolites and TPMT activity in order to adjust dosage and avoid side effects is not routinely performed since only 0.3% of the general population demonstrate absent or extremely low TPMT activity. However, where available, such measurements may be useful in guiding dose optimisation when remission has not been achieved.[42] Treatment with azathioprine and 6-MP should be maintained for several years due to the high relapse rate when these drugs are discontinued.[43]

Methotrexate can be used as an alternative immunomodulator, although its use is limited because of teratogenic effects during pregnancy, as well as an impractical route of administration. Methotrexate is best administered intramuscularly or subcutaneously at a weekly dose of 25 mg for 16 weeks followed by a maintenance dose of 15 mg/week. There are no randomised controlled trials comparing different dosing regimens and routes of administration, although oral methotrexate seems less efficacious. However, for practical reasons oral dosing is more convenient and preferred by patients. No controlled data exist regarding the optimal duration of methotrexate therapy.[44,45]

Question 5i: Monitoring efficacy

5(i). How should efficacy of a treatment be monitored clinically and biologically? What is the definition of treatment failure? When should the effect of treatment be evaluated?
1. Assess remission status/treatment success using clinical signs and symptoms together with normal biological markers (CRP, faecal calprotectin). Endoscopy and imaging techniques can also be used to determine inflammation objectively or when response to treatment is unclear. The CDAI and Harvey Bradshaw Index can be used to quantify clinical efficacy, although opinion differs regarding the relative utility of these tools in everyday practice.
2. Assessment of azathioprine metabolite levels is useful in making management decisions and to identify non-compliant patients or assess non-responders.
3. Trough levels of anti-TNF agents may be useful for identifying the cause of non-response.
4. Treatment failure may be defined after the appropriate period of therapy as:
i. Lack of symptomatic response
ii. Lack of improvements in biological markers
iii. Lack of corticosteroid-free remission
iv. Inflammation, signs of mucosal ulceration with endoscopy or imaging
5. Clinical response/treatment failure should be assessed at:
i. Thiopurines or methotrexate: not earlier than 3 months, not later than a maximum period of 6 months
ii. Anti-TNFs: at a maximum period of 14 weeks (6–14 weeks) after starting therapy
iii. If mucosal healing is to be assessed, this should be performed between 6 and 12 months
79% agreement after 1st vote

Although the CDAI correlates poorly with healing of inflammation by corticosteroids,[15] in the era of biologics and immunomodulators it has been repeatedly shown to reflect disease activity at the mucosal level, albeit imperfectly.[46] There are similarly well-validated endoscopic scores for assessment of Crohn's disease activity such as the Crohn's Disease Endoscopic Index of Severity[47] and Simple Endoscopic Score for Crohn's Disease.[48] For fistulising disease, the presence of draining fistulae or the need for surgical intervention is an appropriate endpoint to measure treatment failure and is easily applied to clinical practice.[49,50] A corticosteroid-free remission seems the most clinically relevant endpoint[51] as the CDAI is a cumbersome tool in a busy clinical environment. The Harvey Bradshaw Index may be a more practical day-to-day tool.[52]

Serum CRP correlates well with disease activity and mucosal healing[53] as well as being predictive of disease response[54] and relapse.[55] However, it correlates less accurately with the activity of small bowel Crohn's disease.[53] Faecal biomarkers of inflammation such as calprotectin and lactoferrin are superior to serum CRP in diagnostic accuracy of intestinal inflammation.[56] Faecal calprotectin concentrations correlate well with mucosal healing in adults and children[57] and an elevated faecal calprotectin is predictive of relapse in those with Crohn's disease in clinical remission.[58] Thiopurine metabolite concentrations may help guide management decisions[59] and the measurement of trough infliximab and adalimumab concentrations may also provide insights into dosing and likelihood of response and failure with these therapies.[60,61]

The timing of clinical assessment will depend on the pharmacological agent. Immunomodulators such as azathioprine and methotrexate may take 3–6 months to achieve full clinical efficacy and mucosal healing.[62] In the context of biological agents, clinical responses can be seen much earlier and assessment at 4–6 weeks has been suggested.[51] Based on ACCENT II (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen)[50] and CHARM (Crohn's trial of the fully Humanised Antibody Adalimumab for Remission Maintenance),[49] assessment for response to treatment of fistulae should take place at weeks 6–14 after starting therapy.

In summary, no particular clinical or biological marker is specific for treatment failure and no specific marker corresponds to mucosal healing. In practice, clinical acumen, judicious use of endoscopy and common laboratory monitoring remain the gold standard of clinical care.

Question 5ii: Assessment of mucosal healing

5(ii). Should mucosal healing be assessed?
1. In the absence of a clinical indication, there is insufficient evidence to recommend the routine assessment of mucosal healing in clinical practice. The assessment of mucosal healing may have a useful role in guiding treatment adjustments.
85% agreement after 1st vote

It has been established that early mucosal healing reduces hospitalisation, long-term remission and need for abdominal surgery,[63] whilst lack of mucosal healing following surgical resection is predictive of clinical relapse.[31]

Corticosteroids are effective in relieving symptoms in Crohn's disease;[4] however, even high-dose corticosteroids induce complete mucosal healing in only 27% of patients.[15] Azathioprine heals the mucosa in 36–70% of patients after up to 3.5 years[46] and is similarly effective following surgical resection.[64] Data on mucosal healing with methotrexate are limited, with rates up to 37.5% reported.[65] Maintenance biological therapy is more effective than episodic treatment in achievement of mucosal healing. Early aggressive therapy with azathioprine and infliximab in the SONIC (Study of Immunomodulator Naïve Patients in Crohn's Disease) trial resulted in higher mucosal healing rates.[66] Early mucosal healing induced by biological agents predicts long-term steroid-free remission[26] and may also predict which patients are able to stop immunomodulator therapy.[67]

In summary, mucosal healing may be an attractive endpoint, but regular endoscopic assessment is impractical and there is insufficient evidence to recommend it in the absence of a clinical indication. Although imperfect, non-invasive markers such as faecal calprotectin have been shown to predict mucosal healing and may be realistic alternatives.[68] Other alternatives include assessment of mucosal healing via magnetic resonance imaging or trans-abdominal ultrasound.[69,70]

Question 6: Combination of azathioprine and an anti-TNF agent

6. If azathioprine and an anti-TNF agent are given in combination, should any of the treatment be stopped? Which treatment should be stopped to achieve the smallest reduction in efficacy? When should that treatment be stopped?
1. When using azathioprine with anti-TNF therapy, the immunomodulator treatment must be individualised according to the individual's treatment and disease status. The benefits of long-term therapy must be weighed against the potential risks for each patient:
i. If the patient has moderately active Crohn's disease and is naïve to immunomodulator therapy, the combination of immunomodulator and infliximab can improve rates of corticosteroid-free remission for up to 1 year
ii. In a patient flaring despite immunomodulator therapy, maintaining the combination of immunomodulator and anti-TNF therapy beyond 6 months may offer no clinical benefit, although this is disputable
iii. There is an increased risk of opportunistic infection with long-term immunomodulator and anti-TNF therapy and of malignancy with thiopurine therapy
iv. There is a small potential risk of hepatosplenic T cell lymphoma (HSTCL) in young adults, particularly young males, with a combination of azathioprine and infliximab or adalimumab
86% agreement after 2nd vote

Apparently conflicting results of recent major clinical trials have confused clinicians. In one study, induction and maintenance therapy with methotrexate and infliximab was shown to have no long-term advantage over infliximab alone.[71] Furthermore, although continuation of azathioprine with infliximab for 2 years resulted in higher trough infliximab concentrations and lower CRP concentrations compared with withdrawal of azathioprine treatment at 6 months, it did not translate into clinical benefits or mucosal healing.[72] Similar findings have been noted for adalimumab[73] and certolizumab.[74] Results from the SONIC trial are apparently at odds with these findings, as the combination of azathioprine and infliximab was found to be superior to infliximab alone in achieving clinical response and mucosal healing in de novo Crohn's disease.[66] An important detail is that patients recruited into SONIC were naïve to immunomodulatory and biological therapy, and represent a different population to the aforementioned studies; however, the findings have been supported by a recent observational study.[75] There are no data on the effect of concomitant immunomodulator withdrawal for certolizumab or adalimumab.

Balancing the very real risk of infection and malignancy against the possible benefits of combination treatment

is the modern challenge for Crohn's disease management. The use of more than two immunomodulators is associated with a higher risk of opportunistic infections[76] and the use of thiopurines is associated with a 5-fold increase in the risk of lymphoma.[77] Of particular concern has been the observation of universally fatal HSTCL in patients treated with the combination of azathioprine and infliximab.[78]

In summary, there is no clear evidence to guide the precise timing of withdrawal of concomitant immunomodulators; however continuation of immunomodulators is reasonable after commencement of a biological agent for refractory disease.

Question 7: Immunomodulator failure

7. If the immunomodulator does not work, what should the approach be? Increase the dosage? Add corticosteroids? Change the immunomodulator? Move to an anti-TNF agent?
1. In any patient with a flare or symptoms rule out infections and complications.
2. In a patient on standard weight-based dose of thiopurines there is no evidence for dose increase.
3. Anti-TNF therapy can be the first consideration in patients who have been on optimal immunomodulator therapy and lost response.
4. If a patient shows intolerance or side effects to purine metabolite immunomodulators, other immunomodulators (methotrexate) or anti-TNF agents may be considered.
83% agreement after 2nd vote

Gastrointestinal infection is an important consideration in the differential diagnosis of acute flares in patients with IBD. It can precipitate a flare, or simply mimic the symptoms (e.g. abdominal pain and diarrhoea). For this reason, it must be ruled out in an immunosuppressed patient who had previously been in remission (based on opinion). In IBD patients receiving an immunomodulator, most commonly azathioprine, there is no evidence to support increasing an already optimised weight-based dose. On the contrary, it may increase the risk of liver injury[79] and myelosuppression, although the latter is also influenced by underlying TPMT activity.[80]

In patients with IBD with a flare of disease activity despite a stable immunomodulator dose, existing evidence strongly supports the addition of anti-TNF therapy. A meta-analysis of 14 randomised, placebo-controlled trials of luminal Crohn's disease, including 3995 patients (most of whom had active disease and were already on immunomodulator therapy) treated with infliximab, adalimumab or certolizumab, demonstrated efficacy in inducing response and remission.[81] In a further analysis of 21 studies including 5356 individuals, anti-TNF therapy did not increase the risk of death, malignancy or serious infection.[81] As mentioned previously, the SONIC study has also shown that combined use of infliximab and azathioprine resulted in better remission rates in Crohn's disease than infliximab alone, and that both the combination and infliximab alone were superior to azathioprine alone.[66] However, increased risk of lymphoma and tuberculosis, although only marginally higher than with azathioprine use, should be discussed with patients before initiating anti-TNF therapy.[77,82]

Adequately designed studies of other immunomodulators in patients failing thiopurine therapy are lacking. Two retrospective studies, published in abstract form only, suggest that methotrexate may have a benefit in clinical response and remission in Crohn's disease, but ultimately, many patients go on to anti-TNF use.[83,84] A retrospective series of mycophenolate mofetil use in Crohn's disease patients failing on azathioprine suggests that, while it may induce remission, its efficacy is limited by a high occurrence of side effects.[85] Overall, there is little evidence to support switching immunomodulators in azathioprine failure.

In patients who demonstrate intolerance to azathioprine, there is an argument for switching to other immunomodulators. Retrospective studies of patients who could not tolerate azathioprine suggests that half or more will be able to tolerate 6-MP and remain on it long term.[86] Furthermore, evidence from case-series and retrospective reviews suggests that patients intolerant to thiopurines may achieve remission with methotrexate and mycophenolate mofetil. Finally, based on their well-established efficacy in the treatment of IBD, anti-TNF agents (either alone, or in combination with another immunomodulator) should be an important consideration in the azathioprine-intolerant patient.

Question 8: Flare-ups with immunomodulators or anti-TNFs

8. If a patient experiences flare-ups when receiving immunomodulators or anti-TNF therapy, should corticosteroids be added?
1. If a patient loses response to an anti-TNF agent, optimisation of therapy should be considered before starting corticosteroids
   i. It is necessary to re-evaluate disease and confirm inflammatory disease before optimising therapy
2. If a patient loses response to immunomodulator therapy, optimisation of therapy and checking compliance should be considered before considering corticosteroids. Avoid use of corticosteroids when failing immunomodulator therapy where possible
   i. Switching to an anti-TNF does not usually require bridging corticosteroids
   ii. If corticosteroids are necessary (e.g. to switch between immunomodulator therapies) dose should be tapered over a period of weeks to limit exposure to their significant side effects
77% agreement after 1st vote

The approach to patients failing immunomodulator therapy was addressed in the previous question. Here, the approach to IBD patients failing anti-TNF therapy is discussed. However, with regard to immunomodulator therapy, it should be reiterated that adding a course of corticosteroids alone, when patients experience a flare on thiopurines, is not recommended, and consideration must be given to starting anti-TNF therapy. While there are no published data to guide the use of corticosteroids in this circumstance, it is often not necessary to give a corticosteroid course when initiating anti-TNF therapy, unless its initiation is going to be significantly delayed and the patient urgently requires treatment (i.e. hospitalised patients). As addressed previously, prolonged corticosteroid use is associated with significant side effects, beyond those of other immunomodulators.

Opinion suggests that repeated corticosteroid use in patients failing on immunomodulator therapy only increases the risk of side effects and is generally not necessary when switching to anti-TNF therapy.

Patients who experience worsening inflammatory activity despite having previously had a good response on an anti-TNF agent do pose a significant challenge for the gastroenterologist. Opinion suggests that it is important to rule out underlying gastrointestinal infections, check compliance with therapy, and verify active disease by laboratory, endoscopic and histological investigations. Once active inflammatory disease has been verified, there is evidence to suggest that doubling the dose of the anti-TNF agent, increasing its frequency of administration, or providing a re-induction regimen can regain response in these patients.[87–90] In addition, randomised studies and a systematic review suggest that approximately 30% of patients failing one anti-TNF agent will achieve sustained remission by switching to another anti-TNF agent.[91–94] Corticosteroid bridging therapy was not employed in any of these studies. There is no direct evidence that corticosteroid use when switching anti-TNF agents improves outcome, and they should not be routinely employed when switching anti-TNF agents or when altering anti-TNF dose or administration schedule. If given, corticosteroids should be limited to a tapering regimen lasting at most 12 weeks, as described in earlier questions.

Question 9: Risk of cancer and infection

9. What are the risks of cancers (all kinds) and infections associated with the short-, mid- and long-term use of immunomodulators and corticosteroids?
1. Although absolute risk is very low, combined use of thiopurines and anti-TNF agents increase the risk of lymphoproliferative disorders.
2. The risk of other malignancies (solid organ tumours) associated with thiopurines and combined thiopurine and anti-TNF therapy still needs to be proven, although there is an increased risk of non-melanoma skin cancer and yearly skin examination should be routinely practised.
3. In most cases, the absolute risk of malignancy remains low; however, the impact of additional risk factors such as young age, Epstein Barr virus status, older age (>65 years), malnutrition, and history of previous malignancy should be taken into account.
4. Immunomodulators and/or corticosteroids and anti-TNF agents are associated with an increased risk of infection. Long-term corticosteroids, but not other immunomodulators, appear to increase risk of perioperative infection. The risk of infection is further increased in older patients, and in patients with co-morbidities and/or malnutrition.
5. The risk of infection in patients with IBD is likely to increase with the number of immunomodulator agents that are used concomitantly, particularly with use of concomitant corticosteroids.
6. The long-term concomitant use of thiopurine and anti-TNF therapy should be carefully considered. In adolescents and young (<35 years) patients (particularly males), combined thiopurine and anti-TNF therapy should be used with caution because of the small risk of HSTCL.
90% agreement after 1st vote

3.1. Lymphoproliferative disorders

The risk of lymphoproliferative disorders has become a major concern for clinicians managing patients with IBD. However, it is difficult to distinguish the possible responsibility of immunomodulator therapy from the background risk due to the inflammatory disorder itself and other confounding factors such as disease severity and disease duration.[95] Since thiopurines are cytotoxic for natural killer and cytotoxic T-cells, their use might be associated with a proliferation of Epstein–Barr virus in infected and immortalised B-cells, eventually leading to a lymphoproliferative disorder. A meta-analysis has shown a pooled relative risk of 4.18 for the development of a lymphoma in patients receiving azathioprine or 6-MP compared with the general population.[96] In a recent French prospective observational cohort study including 19,486 patients with IBD, lymphoproliferative disorders were observed more frequently in patients receiving thiopurines compared with patients who had never received these drugs (hazard ratio 5.28).[77] Similar data were observed in a UK population-based case–control study.[97] Whether the risk of lymphoproliferative disorder is also increased in patients with IBD receiving methotrexate is currently unknown, mainly due to its restricted use in IBD.

A specific lymphoproliferative disorder which has received great attention in the past 5 years is HSTCL. Since the introduction of infliximab, several cases of fatal HSTCL have been described, mainly in young males.[98] The majority of these patients were receiving concomitant immunomodulator agents, but some cases of HSTCL have been described in patients with IBD under thiopurine analogues alone. A policy of minimising the concomitant use of thiopurine and biological agents in patients with IBD, particularly in the apparently high-risk group of adolescents and young (male) adults, is often advocated.[95]

3.2. Solid organ cancers

In the UK population-based case–control study mentioned above, overall cancer risk was not increased in patients receiving azathioprine.[97] However, more recently, thiopurine analogues have been associated with the development of non-melanoma skin cancer in patients with IBD.[99] The incidence of non-melanoma skin cancer in an American case–control trial was higher among patients with IBD compared with controls, and both recent and persistent thiopurine use were associated with non-melanoma skin cancer.[99] Although not evidence-based, yearly skin examination by a trained dermatologist seems mandatory.

3.3. Infections

In the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry, 6290 patients with Crohn's disease were prospectively followed in several North American centres.[22] The majority of patients were treated with immunomodulators (azathioprine, 6-MP or methotrexate). The study found that corticosteroids were independently associated with the development of serious infections, but there was no association with immunomodulators.

In a case–control study, including 100 consecutive patients with IBD with an opportunistic infection and 200

matched IBD controls, the use of corticosteroids, thiopurines and infliximab was associated with significantly increased odds for opportunistic infections, with a considerably higher risk associated with the use of two or three agents versus one agent.[100] The type of infection was different for the three drugs and the absolute number of events was relatively low. However, the use of concomitant corticosteroids in particular increased the infection risk. In a Belgian single-centre cohort study, concomitant treatment with corticosteroids was the only independent risk factor for infections.[101] The interim analysis of the European National Crohn's Observational Registry (ENCORE) showed a similar increased risk for serious infections in patients under prednisone.[102]

Finally, a recent meta-analysis, including seven observational studies involving 1532 patients with IBD, showed an increased risk of postoperative infectious complications in patients receiving corticosteroids.[103] In a Belgian cohort evaluating complications after pouch surgery, a moderate-to-high dose of corticosteroids ($\geq$20 mg methylprednisolone for $\geq$2 months) was associated with postoperative infectious complications, while the use of infliximab was not.[104]

Question 10: Optimal safety monitoring

10. What is the optimal safety monitoring (clinical, laboratory, radiological) of patients receiving immunomodulators or corticosteroids? How often?
1. There may be severe myelosuppression in all patients receiving immunomodulator therapy
i. TPMT analysis (where readily available) may identify those with low TPMT activity at greatest risk of severe haematological complications
ii. Also consider a gradual dose increase starting with 1 mg/kg azathioprine (0.5 mg/kg mercaptopurine), with regular (1–2 weekly) blood count monitoring until target dose is achieved
iii. Patients should be informed about the risks (including pancreatitis) and proper diagnostic steps should be performed when appropriate
2. In addition to clinical safety monitoring, carry out regular monitoring of full blood count and liver function tests in all patients receiving thiopurines and methotrexate. For example, before initiating therapy, every 1–2 weeks during the first month, monthly up to 3 months, and then every 3 months
i. In patients with persistently elevated liver function tests under methotrexate therapy, methotrexate should be stopped and liver biopsy considered (American College of Rheumatology guidelines[105])
3. In addition, take the following measures in patients initiating or taking immunomodulators:
i. Follow guidelines for the prevention of opportunistic infections in IBD (e.g. ECCO consensus[106] and US guidelines[107])
– Vaccinations
– Pap smear for females receiving thiopurines
ii. Solar protection for patients receiving thiopurines, including regular dermatological screening for long-term thiopurine use
iii. Seek urgent medical advice for clinical signs of fever, severe infections, unexplained symptoms, including neurological
4. Patients receiving high doses of corticosteroids should also undergo clinical monitoring, paying particular attention to the risk of opportunistic infection, intra-abdominal abscesses, perforations, hypertension, diabetes (or worsening diabetes) and ophthalmological complications (glaucoma)
i. There is no evidence to support a particular method of monitoring
ii. Calcium and vitamin D supplementation should be considered
97% agreement after 2nd vote

3.4. Optimal safety monitoring of patients receiving immunomodulators

Thiopurine-related adverse events occur in 5–40% of patients in both a dose-dependent and a dose-independent, idiosyncratic manner. These adverse events lead to therapy discontinuation in up to 26% of treated patients.[108] Approximately 89% of the general population has wild-type TPMT, which is associated with normal or high TPMT enzyme activity, while 10% are heterozygous and display intermediate activity.[109] Most importantly, 0.3% of the general population are homozygous for low-activity TPMT alleles and display no detectable TPMT activity, which causes 6-MP to be preferentially metabolised to produce high concentrations of 6-thioguanine, which then leads to bone marrow suppression.

Genotyping the three most common single nucleotide polymorphisms (G238C for TPMT*2, G460A and A719G for TPMT*3A, TPMT*3B and TPMT*3C) or measuring the enzyme activity are two methods for predicting the risk of haematopoietic toxicity. TPMT enzymatic activity can be measured in red blood cells with a radiochemical or high-performance liquid chromatography assay.[110] There is no consensus yet that TPMT genotype or phenotype should be measured before starting azathioprine or 6-MP treatment in patients with IBD, since 73% of patients with severe bone marrow suppression do not carry a TPMT mutation.[111]

Some investigators suggest that thiopurine agents should be avoided entirely in patients with low TPMT activity (heterozygotes); however, it seems that most patients with low TPMT activity can be treated safely with 50% of the normal azathioprine or 6-MP dose provided they are closely monitored.[112] Homozygous or compound heterozygous patients with no TPMT activity should not receive the drug. Importantly, patients with no TPMT mutations or normal TPMT activity, who can receive full dose azathioprine or 6-MP from the start, also require regular full blood count monitoring.[110]

Nodular regenerative hyperplasia is a rare but potentially severe complication of azathioprine in patients with IBD. A systematic survey of patients with IBD followed at 11 European centres identified 37 cases of nodular regenerative hyperplasia, of whom 14 developed complications of portal hypertension.[113] In a US study, 33% of asymptomatic patients with IBD treated with 6-thioguanine and with normal biological results were shown to have nodular regenerative hyperplasia at liver biopsy.[114] Clinicians should be aware of this complication and should monitor liver function tests and platelet counts closely.[113]

In patients receiving methotrexate, measurement of full blood count and liver function tests are advisable before and within 4 weeks of starting therapy, then monthly to

every 3 months thereafter.[1] A similar schedule can be applied for patients receiving thiopurines, although no evidence-based data are available.

Patients initiating or taking immunomodulators should receive proper vaccinations and Pap smears.[106] Furthermore, solar protection is warranted in patients receiving thiopurines. Finally, patients should seek urgent medical advice for clinical signs of fever, severe infections, and unexplained symptoms including neurological symptoms.

3.5. Optimal safety monitoring of patients receiving corticosteroids

Patients with IBD, especially Crohn's disease, are at increased risk of osteopenia and osteoporosis compared with the general population.[115] Several factors have been implicated in the high rate of osteopenia and osteoporosis in these patients, including corticosteroid use, relative malnutrition, and the presence of a chronic inflammatory state. Therefore, calcium and vitamin D supplementation should be considered. Particular attention towards intra-abdominal abscesses, perforation, hypertension, diabetes and ophthalmological complications is warranted. However, there is no evidence to support a particular method of monitoring.

Table 1 Key programme outcomes.

Do…	Do not…
Identify patients with poor prognosis	
Intervene early with immunomodulators and optimise dosing early	
Make corticosteroid-free remission a goal	Do not use prolonged or repetitive courses of corticosteroids or underestimate corticosteroid toxicity
Achieve a balance between clinical benefit and safety when intensifying or prolonging therapy or combining different agents	
Reassess patients at appropriate time points (prednisone at 2–4 weeks; azathioprine 10–12 weeks)	Do not prolong the use of azathioprine at standard doses if full remission is not achieved
Treat beyond symptoms (biomarkers, mucosal healing)	

4. Conclusions

Key strengths of the IBD Ahead 2010 programme were that it provided extensive research into the everyday problems faced by practising gastroenterologists, conducted a comprehensive evaluation of the evidence base, and supplied practical answers based on both evidence and the experience of approximately 600 gastroenterologists from 36 countries. Overall, the programme found that many doctors who manage patients with Crohn's disease lack evidence about basic aspects of corticosteroid and immunomodulator use such as dosage, timing and duration of therapy, safety and choice of drug or regimen, including when to switch agent. In addition, they have questions about more general aspects of the management of Crohn's disease, including the most appropriate ways to define and monitor treatment efficacy or lack of response. There are considerable variations in clinical practice, as has been observed previously.[116]

Despite these differences, the gastroenterologists involved in discussions to provide answers to the questions were able to reach broad agreement on practically-based answers. Key outcomes from the programme (Table 1) included the importance of identifying patients with a poor prognosis and the need to intervene early with an optimal dose of immunomodulators. There was clear agreement that corticosteroid-free remission is an important goal and that corticosteroid toxicity means that prolonged or repetitive courses must be avoided. The importance of achieving a balance between clinical benefit and safety when intensifying or prolonging therapy or combining different agents was another key point. The need to re-assess patients at appropriate time points and change therapy or dose if required was also highlighted. Finally, gastroenterologists also recognised the value of moving towards treatment beyond symptoms and considering the role of mucosal healing and use of biomarkers.

It must be highlighted that this programme was not intended to provide formal guidance on the management of Crohn's disease, and in particular, it cannot supplant existing national and international guidelines. The programme had limitations. Although answers were voted upon using a recognised methodology, consolidation of the feedback into the final answers was achieved mainly through informal discussion rather than by formal consensus methods. Many issues highlighted in the market research phase could not be taken forward to later stages of the programme. The design of the programme allowed incorporation of personal experience into development of the answers; thus the answers were not purely evidence-based. This could be regarded as both a strength and a weakness.

In summary, few high-quality data on conventional therapies exist, and many questions remain unanswered. However, data are becoming available on new treatment objectives which will perhaps lead to a better consensus on these issues in the future. We hope that this educational programme will go some way towards providing practical answers to the many unanswered questions.

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References

1. Dignass A, van Assche G, Lindsay JO, Lemann M, Soderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollon F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010;**4**:28–62.
2. van Assche G, Dignass A, Panes J, Beaugerie L, Karagiannis J, Allez M, Ochsenkuhn T, Orchard T, Rogler G, Louis E, Kupcinskas L, Mantzaris G, Travis S, Stange E. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *J Crohns Colitis* 2010;**4**:7–27.
3. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. *Am J Gastroenterol* 2009;**104**:465–83.
4. Summers RW, Switz DM, Sessions JTJ, Becktel JM, Best WR, Kern FJ, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;**77**: 847–69.
5. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995;**37**:674–8.
6. Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995;**332**:292–7.
7. Donor breast milk banks: the operation of donor breast milk bank services. National Institute for Health and Clinical Excellence. www.nice.org.uk/guidance/CG93 Accessed August 6, 2011, at.
8. Feverish illness in children: assessment and initial management in children younger than 5 years. National Institute for Health and Clinical Excellence. www.nice.org.uk/guidance/CG47 Accessed August 6, 2011, at.
9. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008:CD006792.
10. Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;**86**: 249–66.
11. Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008:CD000296.
12. Tromm A, Bunganic I, Tomsova E, Tulassay Z, Lukas M, Kykal J, Batovsky M, Fixa B, Gabalec L, Safadi R, Kramm HJ, Altorjay I, Lohr H, Koutroubakis I, Bar-Meir S, Stimac D, Schaffeler E, Glasmacher C, Dilger K, Mohrbacher R, Greinwald R. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. *Gastroenterology* 2011;**140**:425–34.
13. Lundin PD, Edsbacker S, Bergstrand M, Ejderhamn J, Linander H, Hogberg L, Persson T, Escher JC, Lindquist B. Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with active Crohn's disease. *Aliment Pharmacol Ther* 2003;**17**:85–92.
14. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkuhn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;**371**:660–7.
15. Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, Rene E. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. *Gastroenterology* 1990;**98**:811–8.
16. Landi B, Anh TN, Cortot A, Soule JC, Rene E, Gendre JP, Bories P, See A, Metman EH, Florent C. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gastroenterology* 1992;**102**:1647–53.
17. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006;**130**:940–87.
18. Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *N Engl J Med* 1994;**331**:836–41.
19. Brignola C, De Simone G, Belloli C, Iannone P, Belluzzi A, Gionchetti P, Campieri M, Barbara L. Steroid treatment in active Crohn's disease: a comparison between two regimens of different duration. *Aliment Pharmacol Ther* 1994;**8**:465–8.
20. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2003:CD000301.
21. Benchimol EI, Seow CH, Otley AR, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009:CD002913.
22. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006;**4**:621–30.

23. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989;**11**:954–63.
24. Bernstein CN, Leslie WD. Therapy insight: osteoporosis in inflammatory bowel disease–advances and retreats. *Nat Clin Pract Gastroenterol Hepatol* 2005;**2**:232–9.
25. Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre JP. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;**8**:244–50.
26. Baert F, Moortgat L, van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010;**138**:463–8.
27. Froslie KF, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007;**133**:412–22.
28. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000;**119**:895–902.
29. Sans M, López-San Román A, Esteve M, Bermejo F, García-Sánchez V, Torres Y. Early use of azathioprine has a steroid sparing effect on recently diagnosed Crohn's disease patients. *Gastroenterology* 2011;**140**(Suppl 1):S109.
30. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006;**130**: 650–6.
31. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;**99**:956–63.
32. Ardizzone S, Maconi G, Sampietro GM, Russo A, Radice E, Colombo E, Imbesi V, Molteni M, Danelli PG, Taschieri AM, Bianchi PG. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology* 2004;**127**:730–40.
33. Hanauer SB, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, Present DH. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004;**127**: 723–9.
34. D'Haens GR, Vermeire S, van Assche G, Noman M, Aerden I, Van Olmen G, Rutgeerts P. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. *Gastroenterology* 2008;**135**: 1123–9.
35. Reinisch W, Angelberger S, Petritsch W, Shonova O, Lukas M, Bar-Meir S, Teml A, Schaeffeler E, Schwab M, Dilger K, Greinwald R, Mueller R, Stange EF, Herrlinger KR. Azathioprine versus mesalazine for prevention of postoperative clinical recurrence in patients with Crohn's disease with endoscopic recurrence: efficacy and safety results of a randomised, double-blind, double-dummy, multicentre trial. *Gut* 2010;**59**:752–9.
36. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg* 2000;**231**:38–45.
37. van Assche G, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, Guslandi M, Oldenburg B, Dotan I, Marteau P, Ardizzone A, Baumgart DC, D'Haens G, Gionchetti P, Portela F, Vucelic B, Soderholm J, Escher J, Koletzko S, Kolho KL, Lukas M, Mottet C, Tilg H, Vermeire S, Carbonnel F, Cole A, Novacek G, Reinshagen M, Tsianos E, Herrlinger K, Oldenburg B, Bouhnik Y, Kiesslich R, Stange E, Travis S, Lindsay J. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis* 2010;**4**:63–101.
38. Sandborn WJ, Tremaine WJ, Wolf DC, Targan SR, Sninsky CA, Sutherland LR, Hanauer SB, McDonald JW, Feagan BG, Fedorak RN, Isaacs KL, Pike MG, Mays DC, Lipsky JJ, Gordon S, Kleoudis CS, Murdock Jr RH. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. North American Azathioprine Study Group. *Gastroenterology* 1999;**117**:527–35.
39. Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2010:CD000545.
40. Prefontaine E, Sutherland LR, Macdonald JK, Cepoiu M. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009:CD000067.
41. Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. *Cochrane Database Syst Rev* 2009:CD006873.
42. Haines ML, Ajlouni Y, Irving PM, Sparrow MP, Rose R, Gearry RB, Gibson PR. Clinical usefulness of therapeutic drug monitoring of thiopurines in patients with inadequately controlled inflammatory bowel disease. *Inflamm Bowel Dis* 2011;**17**: 1301–7.
43. Treton X, Bouhnik Y, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, Cosnes J, Lemann M. Azathioprine withdrawal in patients with Crohn's disease maintained on prolonged remission: a high risk of relapse. *Clin Gastroenterol Hepatol* 2009;**7**:80–5.
44. Patel V, Macdonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009:CD006884.
45. Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Database Syst Rev* 2005:CD003459.
46. Lemann M, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, Modigliani R, Bouhnik Y. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005;**128**: 1812–8.
47. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989;**30**: 983–9.
48. Daperno M, D'Haens G, van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, Rutgeerts P. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;**60**:505–12.
49. Colombel JF, Schwartz DA, Sandborn WJ, Kamm MA, D'Haens G, Rutgeerts P, Enns R, Panaccione R, Schreiber S, Li J, Kent JD, Lomax KG, Pollack PF. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut* 2009;**58**:940–8.
50. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876–85.
51. Clark M, Colombel JF, Feagan BC, Fedorak RN, Hanauer SB, Kamm MA, Mayer L, Regueiro C, Rutgeerts P, Sandborn WJ, Sands BE, Schreiber S, Targan S, Travis S, Vermeire S. American Gastroenterological Association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease, June 21–23, 2006. *Gastroenterology* 2007;**133**:312–39.
52. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;**1**:514.
53. Solem CA, Loftus Jr EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with

clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. *Inflamm Bowel Dis* 2005;**11**: 707–12.
54. Louis E, Vermeire S, Rutgeerts P, De Vos M, Van Gossum A, Pescatore P, Fiasse R, Pelckmans P, Reynaert H, D'Haens G, Malaise M, Belaiche J. A positive response to infliximab in Crohn disease: association with a higher systemic inflammation before treatment but not with -308 TNF gene polymorphism. *Scand J Gastroenterol* 2002;**37**:818–24.
55. Consigny Y, Modigliani R, Colombel JF, Dupas JL, Lemann M, Mary JY. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. *Inflamm Bowel Dis* 2006;**12**:551–7.
56. Langhorst J, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. *Am J Gastroenterol* 2008;**103**:162–9.
57. Canani RB, Terrin G, Rapacciuolo L, Miele E, Siani MC, Puzone C, Cosenza L, Staiano A, Troncone R. Faecal calprotectin as reliable non-invasive marker to assess the severity of mucosal inflammation in children with inflammatory bowel disease. *Dig Liver Dis* 2008;**40**:547–53.
58. D'Inca R, Dal Pont E, Di Leo V, Benazzato L, Martinato M, Lamboglia F, Oliva L, Sturniolo GC. Can calprotectin predict relapse risk in inflammatory bowel disease? *Am J Gastroenterol* 2008;**103**: 2007–14.
59. Wright S, Sanders DS, Lobo AJ, Lennard L. Clinical significance of azathioprine active metabolite concentrations in inflammatory bowel disease. *Gut* 2004;**53**:1123–8.
60. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol* 2006;**4**:1248–54.
61. Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, Claes K, Coopman T, Van Schuerbeek N, van Assche G, Vermeire S, Rutgeerts P. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology* 2009;**137**:1628–40.
62. D'Haens G, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. *Gastrointest Endosc* 1999;**50**:667–71.
63. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:1295–301.
64. D'Haens G, Geboes K, Ponette E, Penninckx F, Rutgeerts P. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. *Gastroenterology* 1997;**112**: 1475–81.
65. Kozarek RA, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med* 1989;**110**:353–6.
66. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.
67. Louis E. Infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors: interim analysis of a prospective cohort study. *Gut* 2008;**57**(Suppl 2):A66.
68. Sipponen T, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Farkkila M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008;**14**: 40–6.
69. Pallotta N, Tomei E, Viscido A, Calabrese E, Marcheggiano A, Caprilli R, Corazziari E. Small intestine contrast ultrasonography: an alternative to radiology in the assessment of small bowel disease. *Inflamm Bowel Dis* 2005;**11**:146–53.
70. Rimola J, Rodriguez S, Garcia-Bosch O, Ordas I, Ayala E, Aceituno M, Pellise M, Ayuso C, Ricart E, Donoso L, Panes J. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. *Gut* 2009;**58**:1113–20.
71. Feagan B, McDonald JW, Panaccione R, Enns RA, Berstein CN, Ponich TP. A randomized trial of methotrexate in combination with infliximab for the treatment of Crohn's disease. *Gastroenterology* 2008;**135**:294–5.
72. van Assche G, Magdelaine-Beuzelin C, D'Haens G, Baert F, Noman M, Vermeire S, Ternant D, Watier H, Paintaud G, Rutgeerts P. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology* 2008;**134**:1861–8.
73. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**:52–65.
74. Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, Schreiber S. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007;**357**: 228–38.
75. Sokol H, Seksik P, Carrat F, Nion-Larmurier I, Vienne A, Beaugerie L, Cosnes J. Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut* 2010;**59**: 1363–8.
76. Viget N, Vernier-Massouille G, Salmon-Ceron D, Yazdanpanah Y, Colombel JF. Opportunistic infections in patients with inflammatory bowel disease: prevention and diagnosis. *Gut* 2008;**57**:549–58.
77. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lemann M, Cosnes J, Hebuterne X, Cortot A, Bouhnik Y, Gendre JP, Simon T, Maynadie M, Hermine O, Faivre J, Carrat F. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;**374**:1617–25.
78. Rosh JR, Gross T, Mamula P, Griffiths A, Hyams J. Hepatosplenic T-cell lymphoma in adolescents and young adults with Crohn's disease: a cautionary tale? *Inflamm Bowel Dis* 2007;**13**:1024–30.
79. Gisbert JP, Gonzalez-Lama Y, Mate J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. *Am J Gastroenterol* 2007;**102**:1518–27.
80. Dubinsky MC. Azathioprine, 6-mercaptopurine in inflammatory bowel disease: pharmacology, efficacy, and safety. *Clin Gastroenterol Hepatol* 2004;**2**:731–43.
81. Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2008;**6**:644–53.
82. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;**7**:874–81.
83. Wahed M, Louis-Auguste J, Baxter L, Limdi J, Lindsay J, McCartney S, Bloom S. Efficacy of methotrexate in Crohns disease patients previously on thiopurine therapy. *Gastroenterology* 2008;**134**(4 suppl 1):A661.
84. Garg M, Wilson J, De Cruz P, Brown S, Kamm M, Connell W, Bell S. Methotrexate in thiopurine refractory Crohn's disease—a

retrospective cohort study. *Gastroenterology* 2008;**136**(5 suppl 1):A657.
85. Palaniappan S, Ford AC, Greer D, Everett SM, Chalmers DM, Axon AT, Hamlin PJ. Mycophenolate mofetil therapy for refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007;**13**:1488–92.
86. Hindorf U, Johansson M, Eriksson A, Kvifors E, Almer SH. Mercaptopurine treatment should be considered in azathioprine intolerant patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2009;**29**:654–61.
87. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut* 2009;**58**:492–500.
88. Schreiber S, Panes J, Mason D, Lichtenstein G, Sandborn W. Efficacy and tolerability of certolizumab pegol are sustained over 18 months: data from PRECISE 2 and its extension studies (PRECISE 3 and 4). *Gastroenterology* 2008;**134**(Suppl 1):A490.
89. Kopylov U, Mantzaris GJ, Katsanos KH, Reenaers C, Ellul P, Rahier JF, Israeli E, Lakatos PL, Fiorino G, Cesarini M, Tsianos EV, Louis E, Ben-Horin S. The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab. *Aliment Pharmacol Ther* 2011;**33**:349–57.
90. Colombel JF, Sandborn WJ, Rutgeerts P, Kamm MA, Yu AP, Wu EQ, Pollack PF, Lomax KG, Chao J, Mulani PM. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: results from the CHARM trial. *Am J Gastroenterol* 2009;**104**:1170–9.
91. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, D'Haens G, Li J, Rosenfeld MR, Kent JD, Pollack PF. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;**146**:829–38.
92. Panaccione R, Sandborn W, D'Haens G, Enns R, Wolf D, Lomax K, Pollack P. Adalimumab maintains long-term remission in moderately to severely active Crohn's disease after infliximab failure: 1-year follow-up of GAIN trial. *Gastroenterology* 2008;**134**(suppl 1):A133–4.
93. Allez M, Vermeire S, Mozziconacci N, Michetti P, Laharie D, Louis E, Bigard MA, Hebuterne X, Treton X, Kohn A, Marteau P, Cortot A, Nichita C, van Assche G, Rutgeerts P, Lemann M, Colombel JF. The efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF antibodies. *Aliment Pharmacol Ther* 2010;**31**: 92–101.
94. Ma C, Panaccione R, Heitman SJ, Devlin SM, Ghosh S, Kaplan GG. Systematic review: the short-term and long-term efficacy of adalimumab following discontinuation of infliximab. *Aliment Pharmacol Ther* 2009;**30**:977–86.
95. D'Haens G, Rutgeerts P. Immunosuppression-associated lymphoma in IBD. *Lancet* 2009;**374**:1572–3.
96. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;**54**:1121–5.
97. Armstrong RG, West J, Card TR. Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study. *Am J Gastroenterol* 2010;**105**: 1604–9.
98. Shale M, Kanfer E, Panaccione R, Ghosh S. Hepatosplenic T cell lymphoma in inflammatory bowel disease. *Gut* 2008;**57**: 1639–41.
99. Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2010;**8**:268–74.
100. Toruner M, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;**134**:929–36.
101. Fidder H, Schnitzler F, Ferrante M, Noman M, Katsanos K, Segaert S, Henckaerts L, van Assche G, Vermeire S, Rutgeerts P. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;**58**:501–8.
102. D'Haens G, Colombel JF, Hommes D, Panes J, Rutgeerts PJ, Ekborn A, Barai U, van Hoogstraten H, Wiekowski M, Antoni C, et al. Corticosteroids pose an increased risk for serious infection: an interim safety analysis of the ENCORE registry. *Gastroenterology* 2011;**135**(Suppl 1):A140.
103. Subramanian V, Saxena S, Kang JY, Pollok RC. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. *Am J Gastroenterol* 2008;**103**:2373–81.
104. Ferrante M, D'Hoore A, Vermeire S, Declerck S, Noman M, van Assche G, Hoffman I, Rutgeerts P, Penninckx F. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009;**15**:1062–70.
105. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, Elkins-Melton M, Outman R, Allison JJ, Suarez AM, Bridges Jr SL, Chatham WW, Hochberg M, MacLean C, Mikuls T, Moreland LW, O'Dell J, Turkiewicz AM, Furst DE. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;**59**:762–84.
106. Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, Domenech E, Eliakim R, Eser A, Frater J, Gassull M, Giladi M, Kaser A, Lemann M, Moreels T, Moschen A, Pollok R, Reinisch W, Schunter M, Stange EF, Tilg H, van Assche G, Viget N, Vucelic B, Walsh A, Weiss G, Yazdanpanah Y, Zabana Y, Travis SP, Colombel JF. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;**3**:47–91.
107. Wasan SK, Baker SE, Skolnik PR, Farraye FA. A practical guide to vaccinating the inflammatory bowel disease patient. *Am J Gastroenterol* 2010;**105**:1231–8.
108. O'Brien JJ, Bayless TM, Bayless JA. Use of azathioprine or 6-mercaptopurine in the treatment of Crohn's disease. *Gastroenterology* 1991;**101**:39–46.
109. Lennard L, Van Loon JA, Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. *Clin Pharmacol Ther* 1989;**46**:149–54.
110. Sandborn WJ. Rational dosing of azathioprine and 6-mercaptopurine. *Gut* 2001;**48**:591–2.
111. Colombel JF, Ferrari N, Debuysere H, Marteau P, Gendre JP, Bonaz B, Soule JC, Modigliani R, Touze Y, Catala P, Libersa C, Broly F. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. *Gastroenterology* 2000;**118**: 1025–30.
112. Kaskas BA, Louis E, Hindorf U, Schaeffeler E, Deflandre J, Graepler F, Schmiegelow K, Gregor M, Zanger UM, Eichelbaum M, Schwab M. Safe treatment of thiopurine S-methyltransferase deficient Crohn's disease patients with azathioprine. *Gut* 2003;**52**:140–2.
113. Vernier-Massouille G, Cosnes J, Lemann M, Marteau P, Reinisch W, Laharie D, Cadiot G, Bouhnik Y, De Vos M, Boureille A, Duclos B, Seksik P, Mary JY, Colombel JF. Nodular regenerative hyperplasia in patients with inflammatory bowel disease treated with azathioprine. *Gut* 2007;**56**:1404–9.

114. Dubinsky MC, Vasiliauskas EA, Singh H, Abreu MT, Papadakis KA, Tran T, Martin P, Vierling JM, Geller SA, Targan SR, Poordad FF. 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. *Gastroenterology* 2003;**125**:298–303.
115. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003;**124**:795–841.
116. Esrailian E, Spiegel BM, Targownik LE, Dubinsky MC, Targan SR, Gralnek IM. Differences in the management of Crohn's disease among experts and community providers, based on a national survey of sample case vignettes. *Aliment Pharmacol Ther* 2007;**26**:1005–18.