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SPECIAL ARTICLE

The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management

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This paper is the second in a series of three publications relating to the European evidence-based consensus on the diagnosis and management of Crohn's disease and concerns the management of active disease, maintenance of medically induced remission and surgery. The aims and methods of the ECCO Consensus, as well as sections on diagnosis and classification are covered in the first paper [van Assche et al. JCC 2009a]. The final paper covers post-operative recurrence, fistulating disease, the management of paediatric and adolescent IBD, pregnancy, psychosomatics, extraintestinal manifestations and complementary or alternative therapy for Crohn's disease [Van Assche et al JCC 2009b].

Principal changes with respect to the 2006 ECCO guidelines

The early use of azathioprine/mercaptopurine or methotrexate in combination with steroids is an appropriate option in moderately active localised ileocaecal CD. Anti-TNF therapy should be considered as an alternative for patients with objective evidence of active disease who have previously been steroid-refractory, steroid-dependent, or steroid-intolerant (based on Statement 5B).

For those patients with severely active localised ileocaecal Crohn's disease and objective evidence of active disease who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option [EL1a, RG B for infliximab]. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate (based on Statement 5C).

All currently available anti-TNF therapies appear to have generally similar efficacy and adverse-event profiles for inflammatory ('luminal') Crohn's disease, so the choice depends on availability, route of delivery, patient preference, cost and national guidelines [EL5, RG D] (Statement 5I).

Patients receiving azathioprine or mercaptopurine who relapse should be evaluated for adherence to therapy and have their dose optimised. Changing their maintenance therapy to methotrexate [EL1b RG B] or anti-TNF therapy [EL1a RGB] should be considered. Surgery should always be considered as an option in localised disease [EL4, RG D] (Statement 6D).

5.0. Medical management of active Crohn's disease

5.1. Introduction

The management plan for a patient with Crohn's disease should take into account the activity, site and behaviour of disease, and should always be discussed with the patient. Determining the activity of disease may be more difficult in Crohn's disease than ulcerative colitis, since symptoms (such as pain or diarrhoea) may be due to causes other than active disease. Therefore, alternative explanations for symptoms such as enteric infection, and abscess, bacterial overgrowth, bile salt malabsorption, dysmotility (IBS), or gall stones should always be considered. Iron deficiency anaemia should be identified and treated, since it may explain symptoms of fatigue or lethargy. Some treatment decisions may have to be made without knowing the full distribution of disease, especially in those patients with severe disease. Experience has shown that clinicians are often poor judges of disease activity; therefore objective evidence of disease activity should be obtained (inflammatory markers or colonoscopy as appropriate) before starting or changing medical therapy. This concept is supported by the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC), in which the benefit of therapy was significantly higher in those patients with endoscopic evidence of active disease at entry to the trial.[1]

The appropriate choice of medication is influenced by the balance between drug potency and potential side-effects; previous response to treatment (especially when considering treatment of a relapse, or treatment for steroid-dependent or -refractory disease); and the presence of extraintestinal manifestations or complications. Different preparations are released at different sites and may have local activity (such as mesalazine preparations and budesonide), so the choice is best tailored to the individual patient. It is important to remember that one option for selected patients with mild disease would be to start no active treatment, as in a systematic review of clinical trials, 18% (95% CI 14–24%) of patients entered remission when receiving placebo alone.[2] Thus it is clearly important to involve patients in all therapeutic decisions.

It should be noted that the numbers of patients in randomized clinical trials with disease at different locations or patterns of behaviour, become too small for statistically valid conclusions to be drawn on these grounds alone, even though it is generally agreed that both factors are important when considering treatment. Sections 5.2 and 5.3 detail the Concensus statements and supporting text for the medical management of active disease at specific sites and in differing scenarios, whereas Section 5.4 covers therapy-specific considerations and the evidence base for individual treatments.

5.2. Treatment according to site of disease and disease activity

5.2.1. Mildly active localised ileocaecal Crohn's disease

ECCO Statement 5A
Budesonide 9 mg daily is the preferred treatment [EL2a, RG B]. The benefit of mesalazine is limited [EL1a, RG B]. Antibiotics cannot be recommended [EL1b, RG A]. No treatment is an option for some patients with mild symptoms [EL5, RG D].

Although the stage at which immunosuppressive and biological therapy is introduced is changing, it is important

to remember that an appreciable proportion of patients with CD have a mild pattern of disease. Thus, in an inception cohort of 843 patients with CD (the IBSEN cohort), diagnosed between 1990 and 1994, only a quarter of the patients were treated with immunomodulators and 4% with anti-TNF agents during the first ten years of follow-up.[3] In another cohort from Olmsted County, Minnesota, USA, 43% of patients were never treated with steroids.[4] Finally, among patients diagnosed and followed up at private hospitals in Germany for a median 39 months, 27% of patients had mild disease that did not need steroids.[5] Despite this, the majority of patients with active CD have symptoms that merit treatment.

Budesonide 9 mg daily is the favoured therapy to induce remission in mildly active, localised ileocaecal Crohn's disease, because it is superior to both placebo (relative risk (RR) 1.96, 95% CI 1.19–3.23) and mesalazine (RR 1.63; 95% CI 1.23–2.16).[6] Budesonide is preferred to prednisolone for mild disease because it is associated with fewer side-effects (RR 0.64, 95% CI 0.54–0.76). However, budesonide is significantly less effective than conventional steroids for induction of remission (RR 0.86, 95% CI 0.76–0.98), particularly among patients with severe disease (CDAI>300) (RR 0.52, 95% CI 0.28–0.95). In individual studies, budesonide achieves remission in 51–60% over 8–10 weeks.[7–12]

Nevertheless, a recent study on budesonide (Budenofalk®) compared to mesalazine for active Crohn's disease, published in abstract form only, found no difference between the two treatments.[13] Remission rates of 69.5% for budesonide and 62.1% for mesalazine were observed in the ITT population in this study. A clinically relevant and statistically insignificant CDAI drop of 100 points was observed in 89% of budesonide-treated patients and in 79% of mesalazine-treated patients. In patients with mild disease (CDAI<300 points) both treatments appeared to be equally effective in this trial. This study was presented in abstract form only after the Consensus meeting in Vienna in 2008 and these preliminary data are in contrast to a previous meta-analysis.[14] This meta-analysis showed no clinically significant effect of mesalazine in the management of mild to moderately active ileocaecal Crohn's disease compared to placebo, although it found a significant reduction in the CDAI in patients with active ileocaecal CD receiving ethylcellulose-coated mesalazine 4 g/day. Since the drop in CDAI was just 18 points compared to placebo (−63 vs −45, $p=0.04$) in 615 patients, the clinical benefit is considered marginal. Lower doses of mesalazine cannot be recommended for active CD. However, the conflicting new data implicate that mesalazine deserves further evaluation for the treatment of mildly active CD. A further study of high-dose (6 g daily) mesalazine for active CD is currently under way. Future meta-analyses should incorporate more recent studies with high-dose formulations.

Antibiotics (metronidazole, ciprofloxacin), with or without mesalazine, are not recommended, because side-effects are commonplace. The same applies to nutritional therapy, which is often poorly tolerated by adults, although there are case series or small trials that have shown these treatments to be modestly effective.

5.2.2. Moderately active localised ileocaecal Crohn's disease

ECCO Statement 5B
Moderately active, localised ileocaecal Crohn's disease should preferably be treated with budesonide 9 mg/day [EL1a, RG A], or with systemic corticosteroids [EL1a, RG A]. Antibiotics can be added if septic complications are suspected [EL5, RG D]. Azathioprine/6-mercaptopurine or methotrexate in combination with steroids is also an appropriate option. Anti-TNF therapy should be considered as an alternative for patients with objective evidence of active disease, who have previously been steroid-refractory, -dependent, or -intolerant. Risks should be carefully considered and discussed with patients [EL1b, RG B].

For moderately active CD, either budesonide or prednisolone are appropriate initial induction therapies. Prednisolone is highly effective, but more commonly causes side-effects than budesonide.[6] In a systematic (Cochrane) review of conventional corticosteroids, two studies compared corticosteroids to placebo and six studies compared corticosteroids to 5-ASA.[15] Corticosteroids were found to be significantly more effective than placebo at inducing remission in CD (RR 1.99; 95% CI 1.51–2.64; $p<0.00001$). Interestingly, there was no difference in the proportion of patients experiencing adverse events with steroids compared to high-dose 5-ASA, and steroids did not induce more study withdrawals due to adverse events than either placebo or 5-ASA. In addition, prednisolone is less expensive than budesonide if cost is an important consideration. The dose of prednisolone is adjusted to the therapeutic response over a period of weeks (see below). A more rapid dose reduction can be associated with early relapse. The Consensus does not favour sole nutritional therapy (Sections 5.2.1 and 5.4.9), antibiotics (unless septic complications are suspected), or surgery for moderately active ileal CD as first-line therapy.

Particular effort should be made to minimise corticosteroid exposure in CD, even though steroids remain (in 2009) the mainstay for treating active disease. Part of the problem is a complete lack of efficacy for maintaining remission (see Section 6.0). No more than one in four patients given corticosteroids to induce symptomatic remission will still be in remission after a year, even if patients' treatment with immunomodulators is included.[16]

An effective approach to minimizing steroid therapy is the early introduction of anti-TNF agents. Selection of patients appropriate for biological therapy depends on clinical characteristics, previous response to other medical therapies, phenotype and co-morbid conditions. Certain patient populations may derive greater benefit from the early introduction of biological therapy, including steroid-refractory (Section 5.3.3) or steroid-dependent patients.[17] However, a study of 133 patients with active Crohn's disease who had not previously received glucocorticoids, antimetabolites, or infliximab also suggested benefit of early biological therapy in this relatively treatment naïve group. This trial randomized patients to either early combined immunosuppression or conventional treatment (commonly referred to as the Step Up/Top Down study).[18] At week 26, 60.0% of 65 patients in the combined

immunosuppression group were in remission without corticosteroids and without surgical resection, compared with 35.9% of 64 controls, giving an absolute difference of 24.1% (95% CI 7.3–40.8, p=0.006). It has now been established (through the SONIC study) that combination treatment with infliximab and azathioprine is more effective than infliximab alone for achieving (and maintaining) steroid-free remission in patients at an early stage of disease.[1] This is addressed in the section on maintaining remission, although the distinction between induction and maintenance therapy is largely one of convenience, since there should be a seamless transition in individual patients. Evidence for the efficacy of individual anti-TNF agents is covered in Section 5.4.4.

5.2.3. Severely active localised ileocaecal Crohn's disease

ECCO Statement 5C
Severely active localised ileocaecal Crohn's disease should initially be treated with systemic corticosteroids [EL1a, RG A]. For those who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option for patients with objective evidence of active disease [EL1a, RG B for infliximab]. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. Surgery is a reasonable alternative for some patients and should also be considered and discussed [EL5 RG D].

The initial treatment of severe ileal CD still includes prednisolone or intravenous hydrocortisone. A substantial change in the therapeutic approach in the past 5 years has been the recognition that it is potentially possible to use clinical criteria at diagnosis to predict the subsequent course of disease (Section 5.3). This, in turn, has affected the threshold for introducing anti-TNF and immunomodulator therapy in patients with markers of poor prognosis. Given that continued treatment with either infliximab or adalimumab has been associated with a substantial reduction (about 30% at 12 months) in surgery and hospitalization for CD,[19,20] the threshold is likely to decrease further. Nevertheless, there are no data that specifically apply to localised ileocaecal disease.

Anti-TNF therapy is still best reserved for patients not responding to initial therapy and for whom surgery is considered inappropriate. However, this does not mean that surgery takes precedence over adalimumab, infliximab, or certolizumab pegol (the latter is not currently licensed for CD in Europe), and the therapeutic strategy for an individual should be a joint decision between patient, physician and surgeon. Although anti-TNF therapy may reduce the need for surgical resection, the threshold for surgery in localised ileocaecal disease is lower than for disease elsewhere. Indeed, some experts still advocate surgery (especially laparoscopic-assisted resection, Section 7.2.6) in preference to anti-TNF therapy for disease in this location. Others advocate resection if medical therapy is not effective within 2–6 weeks. It is now clear when starting anti-TNF therapy in patients with CD naïve to immunosuppression, that combination therapy with infliximab and azathioprine is more effective than either alone, whether for induction of remission, maintenance of remission up to 1 year, or for mucosal healing.[1] However, only patients with an elevated serum CRP or the presence of mucosal lesions at colonoscopy gained additional benefit from infliximab therapy. The combination of infliximab and azathioprine was not superior to infliximab alone in the subgroup of patients with active signs of inflammation. It is unknown whether combination therapy with anti-TNF agents other than infliximab would also improve outcome in patients naïve to immunosuppressives other than steroids.

It may sometimes be difficult to distinguish between active disease and a septic complication, but antibiotics should be reserved for patients with a temperature or focal tenderness, or in whom imaging has indicated an abscess. Adding ciprofloxacin and metronidazole to budesonide has shown no advantage over budesonide alone in active Crohn's disease.[21]

5.2.4. Colonic disease

ECCO Statement 5D
Active colonic CD may be treated with sulfasalazine if only mildly active [EL1b, RG A], or with systemic corticosteroids [EL1a, RG A]. For those who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option for patients with objective evidence of moderate or severely active disease [EL1a, RG B for infliximab]. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. Before initiating immunomodulator or anti-TNF therapy, surgical options should also be considered and discussed [EL5, RG D].

It is easier to confirm the activity and severity of colonic CD than it is for isolated small bowel disease, even though active ileal disease is accessible to ileocolonoscopy in the large majority of patients. This may explain why colonic disease appears to respond better to anti-TNF therapy than ileal disease.[22] Systemic corticosteroids such as prednisolone or equivalent are effective,[23,24] whereas budesonide, in its current formulation, has no role in treating colonic disease, unless it primarily affects the proximal colon. Therefore steroids remain first-line therapy, with immunomodulators as steroid-sparing agents for those who have relapsed. As with disease in any location, the decision needs to take account the previous response to therapy and the pattern of disease: if there is infrequent relapse and a previous rapid response to steroids, then it is reasonable to take this conventional approach.

On the other hand, it is important that the expectations of gastroenterologists and their patients are appropriate: it is no longer acceptable for patients to be subjected to recurrent cycles of steroids when effective therapy for achieving and maintaining steroid-free remission with anti-TNF therapy exists. If symptoms persist in spite of steroids (with or without immunomodulators), disease activity should be assessed endoscopically and anti-TNF therapy commenced if activity is demonstrated (Section 5.3.2). If patients do not respond or lose response to anti-TNF therapy, then surgery is generally appropriate (Section 7.3). Occasionally colonic disease is so

severe and aggressive (often in combination with perianal sepsis) that surgery to defunction the colon is necessary for symptom control before anti-TNF therapy can be used safely.

The use of sulfasalazine, metronidazole,[25] or nutritional therapy[26] for adults with colonic CD has almost been consigned to history. Sulfasalazine 4 g daily is modestly effective for active colonic disease,[23,24] but it cannot be recommended in view of a high incidence of side-effects. There is no evidence that mesalazine is effective for active colonic CD, but opinion still varies about the value of topical mesalazine as adjunctive therapy in left-sided colonic CD. Topical mesalazine can be considered in distal colonic CD, but a similar proportion advise or recommend it as do not use it.

5.2.5. Extensive small bowel disease

ECCO Statement 5E
Extensive small bowel Crohn's disease should be treated with systemic corticosteroids and thiopurines or methotrexate [EL5, RG D]. For patients who have relapsed, anti-TNF therapy with or without azathioprine is an appropriate option if there is objective evidence of moderate or severely active disease [EL5, RG D]. Adjunctive nutritional support is appropriate [EL4, RG C]. Surgical options should also be considered and discussed at an early stage.

ECCO Statement 5F
Patients who have clinical features that suggest a poor prognosis currently appear to be the most suitable patients for early introduction of thiopurines, methotrexate and or anti-TNF therapy [EL5 RG D].

The inflammatory burden is greater in extensive (>100 cm) than in localised small bowel disease, often resulting in nutritional deficiencies. Treatment with steroids and the early introduction of concomitant immunomodulators (for their steroid-sparing effect) is considered appropriate. Nutritional support should be given as an adjunct to other treatment, and may be considered as primary therapy if disease is mild.[26] However, early introduction of anti-TNF therapy should also be considered, especially in who have clinical indicators of poor prognosis (Section 5.3), as several analyses have shown that anti-TNF therapy is more effective when treatment is initiated early in the disease. Thus, in the CHARM trial with adalimumab, clinical remission rates approached 60% in patients who had CD for <2 years, compared to 40% ($p<0.05$) in patients who had a longer duration of disease.[27] A similar phenomenon was observed in patients who received infliximab as first-line treatment, for whom >90% of patients had a clinical response after the first administration.[18] The same is also true for certolizumab pegol.[28] However, the most compelling evidence in favour of early intervention, comes from a pilot trial in the post-operative phase of CD: 10/11 (91%) of patients treated with infliximab after ileocolic resection had no endoscopic recurrence after 1 year,[29] compared to 2/13 (15%, $p=0.0006$) treated with placebo infusions. It is important to note that these data are taken from studies that either included only a small number, or formally excluded patients with extensive disease. However, common sense indicates that the management of patients with extensive small bowel disease should be more aggressive given the well documented adverse consequences.[30]

In patients with extensive small bowel disease, surgical resection risks creating a short bowel. However, nutritional support with or without anti-TNF therapy prior to multiple strictureplasty is a valid strategy. Surgery, especially strictureplasty, is more appropriate for long-standing, isolated and fixed strictures. Careful consideration should be given to the optimal approach to preventing recurrence (Section 8). Anti-TNF therapy or conventional immunomodulators may be appropriate, depending on the time interval from previous surgery, or the time from diagnosis to first surgery as these factors may predict the aggressiveness of CD that post-operative therapy is designed to modify.

5.2.6. Oesophageal and gastroduodenal disease

ECCO Statement 5G
Oesophageal or gastroduodenal Crohn's disease may best be treated with a proton pump inhibitor [EL5, RG D], if necessary together with systemic corticosteroids [EL4, RG C] and thiopurines or methotrexate [EL4, RG D]. Anti-TNF therapy is an alternative for severe or refractory disease [EL4, RG D]. Dilatation or surgery is appropriate for obstructive symptoms [EL4, RG C].

Upper gastrointestinal (GI) tract inflammation in Crohn's disease is increasingly diagnosed as patients more frequently undergo upper GI endoscopy. There may be no localizing symptoms and although the Montréal classification identifies upper GI involvement as a subgroup, independent of other locations, a consensus on what qualifies as significant 'involvement' is lacking. Reported incidence data vary considerably depending on the definitions used and the population studied. Paediatric data suggest that upper GI endoscopy is useful in differentiating CD from ulcerative colitis when inflammation is otherwise predominantly confined to the colon; however, this question has yet to be studied in adults.[31] Controlled trials of individual therapies are lacking despite the finding that Crohn's disease in the proximal gut is associated with a worse prognosis.[32] Evidence-based therapy is mainly derived from case series.[33,34] Most would add a proton pump inhibitor to conventional induction therapy and have a lower threshold for starting anti-TNF therapy than for disease elsewhere, given the poor prognosis.

5.3. Treatment according to the course or behaviour of disease

A novel target for both clinical trials and the management of individuals with CD is the desire to change the pattern of future disease. Therefore, a concerted effort is being made to identify those patients with a poor prognosis who might benefit most from the early introduction of immunomodulator or biological

therapy. However, it has been difficult to identify reliable risk factors that predict a poor disease outcome. Early series showed that smoking had an adverse effect on the disease course, particularly with regard to post-operative recurrence in women.[35] Young patients and those with extensive small bowel CD were found to have a 3- to 7-fold increase in mortality in a population-based study.[30] The trouble is that these studies have neither been designed nor had sufficient power to relate outcome to the original patient phenotype.[36]

Clinical features at diagnosis can now be associated with the course of disease over the following 5 years, although whether treatment decisions based on this information can alter this outcome remains to be tested. In 2006, a French group reported a retrospective study of 1188 patients and identified features associated with the development of 'disabling disease'.[37] Disabling disease was defined as the condition of patients who needed treatment with more than two courses of steroids, who were hospitalised, needed immunomodulators, or who came to surgery within 5 years of diagnosis. Factors *at diagnosis* that were associated with this outcome included young age (<40 years), initial need for steroid therapy and the presence of perianal disease. The authors validated their retrospective study with the prospective follow-up of 302 patients from 1998. If two of the criteria were present at diagnosis, then 84% (91% in the retrospective cohort) had 'disabling disease' by 5 years and if all three risk factors were present, then the figures were 91% and 93% respectively. In spite of disproportionately large numbers with 'disabling disease' in this hospital based population, it defines a measure against which treatment to alter the pattern of disease can be assessed. In fact, the criteria for 'disabling disease' were also validated in a population-based cohort from Olmsted County, Minnesota. In this cohort of 72 patients diagnosed between 1983 and 1996 and followed for at least 5 years, 54% had 'disabling disease'.[38]

The rationale for using these criteria in clinical practice is that most have now been independently confirmed.[38,39] In an independent cohort, a more restrictive category of 'severe disease' was defined[39] as the development of complex perianal disease, any colonic resection, two or more small bowel resections or the construction of a definitive stoma within 5 years of diagnosis. The prevalence of 'severe disease' within 5 years of diagnosis in their series of 361 patients was 37%. Perianal disease, young age of onset and need for initial steroids were confirmed, but stricturing disease behaviour and loss of >5 kg weight before diagnosis, were also independently associated with the development of severe disease.

Consequently, patients presenting at a young age, with extensive disease, needing initial treatment with steroids, or with perianal disease *at diagnosis* can be considered to have a poor prognosis. This should inform discussion with the patient and is increasingly taken into account in therapeutic decision making. Treatment decisions will also differ between patients at initial presentation and subsequent relapse, depending on the pattern of relapse and previous response to therapy. Therefore, patients who have active disease that persists in spite of appropriate initial steroid therapy are best considered as a separate group with steroid-refractory disease (see Definitions). It is helpful when considering a management strategy to recognise other treatment-refractory groups, such as immunomodulator-refractory, or anti-TNF therapy-refractory. No definitions have yet been agreed, but such patients represent an important group of patients who deserve study.

5.3.1. Treatment of relapse compared to newly diagnosed disease

The initial treatment of relapse should be based upon previously successful therapies. However, consideration should be given to other factors including patient preference (adverse effects, necessary speed of response, convenience, etc), the time to relapse, concurrent therapy (whether a relapse occurred during treatment with immunomodulators) and adherence to therapy.

5.3.2. Early relapse

Any patient who has an early relapse (defined as an arbitrary period of <3 months) should be started on an immunomodulator to reduce the risk of a further relapse. Opinion remains divided whether to use the same treatment to induce remission and taper more slowly or use more potent induction therapy. It is important to confirm disease activity as a cause of recurrent symptoms, although unnecessary to re-evaluate the distribution of disease unless this will alter medical or surgical management. Patients who have a relapse of moderate or severe activity should be considered for anti-TNF therapy, since infliximab is more effective than azathioprine in early (duration <2 years), treatment-naïve patients with CD and there is a significant advantage in using the combination of infliximab and azathioprine.[1] All anti-TNF agents are more effective when introduced at an early stage (as discussed above).

5.3.3. Steroid-refractory Crohn's disease

ECCO Statement 5H
Patients with objective evidence of active disease refractory to corticosteroids should be treated with anti-TNF therapy, with or without thiopurines or methotrexate [EL1a, RG B for infliximab], although surgical options should also be considered and discussed at an early stage.

For active CD that is refractory to steroids, local complications (such as an abscess) should be excluded by appropriate imaging and other causes of persistent symptoms considered. If active CD is confirmed, anti-TNF therapy is appropriate. If patients with CD are naïve to immunosuppression, treatment can follow the guidance in Section 5.2.3; see also Section 6.2.7. For patients with established CD who have active disease despite therapy with immunomodulators, post-hoc subgroup analyses of the major trials with all three anti-TNF agents have not demonstrated significant differences in efficacy between patients receiving the biologic plus concomitant immunomodulator and those treated with the biologic alone. It must, however, be remembered that these are subgroup analyses in patients that had already failed immunomodulator therapy and the studies were not designed to answer this question. Current data suggest that the effect of continuing immunomodulator therapy on reducing immunogenicity in patients receiving

biologic therapy is more pronounced in patients undergoing episodic biologic therapy — a strategy that has largely been abandoned where possible, due to lesser efficacy. It is reasonable to conclude that in the majority of patients given biologics, immunosuppression should not be continued for the sole reason of decreasing antibody production, although anti-drug antibodies are not the only factor that governs the immunogenicity of a compound.[40]

It is also possible that the combination of steroids with an anti-TNF agent and an immunomodulator may improve outcome. In a randomized, double-blind, placebo-controlled trial, patients who had initiated corticosteroids within the last 6 weeks were randomized 1:1 to receive infliximab and placebo ($n=63$), or infliximab and methotrexate 25 mg subcutaneously each week ($n=63$).[41] At week 14, there were no differences in the percentage of patients in steroid-free remission between the 2 groups (76% and 77%). Although this can be interpreted as a failure of methotrexate to offer additional benefit to infliximab, the very high rate of steroid-free remission (twice that seen in other studies) is notable.

The timing of surgery depends on the severity of symptoms, inflammatory burden and considerations above (Sections 5.2.3 and 5.2.4). The patient's views and extent of disease should also be taken into account. Nutritional therapy is an appropriate adjunctive, but not sole, therapy.

5.4. Therapy-specific considerations

The therapeutic goal should be to induce clinical remission for every patient, but even at diagnosis it is essential to keep in mind how remission will be maintained after medical induction therapy. In clinical practice, a 'step-up' approach of adding therapies if first-line or less toxic approaches are unsuccessful within an appropriate period, is commonly used.[42] However, decisive treatment with a potent agent ('top-down' approach) at an early stage may be preferred by the patient suffering symptoms from active disease.[18] The choice of an induction agent depends on published efficacy, side-effect profile and familiarity, as well as the patient's views in conjunction with the activity, location and behaviour of disease (as outlined above).

5.4.1. Aminosalicylates

5.4.1.1. Efficacy of aminosalicylates. Initially published trials showed oral aminosalicylates to be an effective treatment for active ileal, ileocolic or colonic CD. Sulfasalazine 3–6 g/day is effective in patients with colonic, but not in those with small bowel disease.[23,24] Asacol 3.2 g/day was effective in ileocolic or colonic disease[43] and Pentasa 4 g/day was reported to be effective for ileitis, ileocolitis and colitis.[44] As a consequence, mesalazine became a popular treatment with limited toxicity for mild disease. However, a meta-analysis of the three placebo-controlled trials of Pentasa 4 g daily for active CD for 16 weeks in a total of 615 patients, showed a mean reduction of the CDAI from baseline of −63 points, compared to −45 points for placebo (delta: 18 points, $p=0.04$).[14] Although this confirmed that a time dependent delayed release formulation of mesalazine, Pentasa 4 g/day, is superior to placebo, the clinical significance of the reduction in CDAI is debatable. Subgroup analyses did not provide sufficiently clear answers to determine whether one group of patients benefits more than another. Consequently at this stage mesalazine should be considered clinically no more effective than placebo for active ileal or colonic Crohn's disease.[45]

5.4.1.2. Adverse effects of aminosalicylates. Side effects of sulphasalazine occur in 10–45% of patients, depending on the dose. Headache nausea, epigastric pain and diarrhoea are most common and dose-related. Serious idiosyncratic reactions (including Stevens Johnson syndrome, pancreatitis, agranulocytosis, or alveolitis) are rare and less common than when the sulfapyridine containing prodrug, sulphasalazine is used for rheumatoid arthritis.[46] Mesalazine intolerance occurs in up to 15% of exposed individuals long term. Diarrhoea (3%), headache (2%), nausea (2%), rash (1%) and thrombocytopenia (<1%) are reported, but a systematic review has confirmed that all currently used 5-ASA agents are safe, with adverse events that are similar to placebo for mesalazine or olsalazine.[47] Acute intolerance in 3% may resemble a flare of colitis since it includes bloody diarrhoea and recurrence on rechallenge may help confirm this diagnosis. Renal impairment (including interstitial nephritis and nephrotic syndrome) is rare and idiosyncratic. A population-based study found the risk (OR 1.60, CI 1.14–2.26) to be associated with disease severity rather than the dose or type of mesalazine.[48]

5.4.1.3. Monitoring. Patients with pre-existing renal impairment, concomitant use of other potentially nephrotoxic drugs, or co-morbid disease should have renal function monitored during 5-ASA therapy. Most clinicians believe that creatinine and full blood count should be monitored every 3–6 months during aminosalicylate therapy, although there is no evidence favouring one monitoring regime over another.

5.4.2. Antibiotics

5.4.2.1. Efficacy. Clinical trials suggest that metronidazole is no better than placebo at inducing remission, but did demonstrate a drop in CDAI of 67–97 points in the metronidazole group compared to 1 point with placebo ($p=0.002$).[49] Patients with isolated small bowel disease showed no benefit, but only 56/105 patients completed the trial, with 17 withdrawing for adverse events. In a 16 week cross-over trial, the response to metronidazole was similar to sulfasalazine (25% remission rates in each arm, no placebo), but more patients who failed sulfasalazine subsequently responded to metronidazole than vice versa.[50]

Ciprofloxacin has shown similar efficacy to mesalazine in active CD, with a response rate of 40–50% after 6 weeks.[51] The combination of ciprofloxacin and metronidazole has been compared with steroids, showing 46% vs 63% remission (ns).[52] Other antibiotics require further testing. A meta-analysis of 6 trials of anti-mycobacterial therapy showed that only the two trials including steroids for induction of remission influenced the disease.[53] A subsequent 216 patient randomized trial conducted in Australia showed that triple therapy in conjunction with steroids improved the response at 16 weeks, although when anti-mycobacterial therapy alone was

continued for 2 years in those who responded the pattern of disease was unchanged over 3 years.[54] At present, antibiotics are only considered appropriate for septic complications, symptoms attributable to bacterial overgrowth, or perineal disease. Anti-mycobacterial therapy cannot be recommended on the evidence from controlled trials.

5.4.3. Corticosteroids

5.4.3.1. Efficacy of steroids. Two major trials established corticosteroids as effective therapy for inducing remission in Crohn's disease. The National Co-operative Crohn's disease Study randomized 162 patients, achieving 60% remission with 0.5–0.75 mg/kg/day prednisone (the higher dose for more severe disease) and tapering over 17 weeks, compared to 30% on placebo (NNT = 3).[23] The comparable 18 week European Co-operative Crohn's Disease Study ($n = 105$) achieved 83% remission on 6-methylprednisolone 1 mg/kg/day compared to 38% on placebo (NNT = 2).[24] The high placebo response rate should be noted, because disease activity in Crohn's disease fluctuates spontaneously and clinical scores have a high subjective content.[2] No formal dose–response trial of prednisolone has been performed. Enteric-coated budesonide 9 mg has consistently shown benefits for active ileal or ileocolic CD, but is less effective (OR 0.69, 95% CI 0.51–0.95) than prednisolone in a Cochrane systematic review.[55]

5.4.3.2. Selection between topically and systemically acting corticosteroids. Efficacy should be balanced against side effects, although decisive treatment of active disease in conjunction with a pre-defined strategy for complete steroid withdrawal may be preferred by the patient. At present, budesonide is advocated in preference to prednisolone if the disease distribution is appropriate (terminal ileal or ileocecal disease — Section 5.2). A standard tapering strategy is recommended, since this helps identify patients who relapse rapidly and therefore need adjunctive therapy with thiopurines. There are no trials between different steroid-tapering regimens and 'standard' regimens differ between centres. Although good at inducing remission, steroids are ineffective at maintaining remission[56] and a long-term treatment strategy to maintain steroid induced remission should be planned at an early stage.

5.4.3.3. Adverse effects of steroids. Three broad groups of adverse events can be identified, although 50% of patients report no adverse events on prednisolone. Budesonide is still associated with steroid-side-effects at a lower (33% vs 55%,[8]) or similar frequency,[10] although less severe than prednisolone.[55] *1) Early effects* due to the supra-physiologic doses used to induce remission in active Crohn's disease include cosmetic (acne, moon face, oedema, and skin striae), sleep and mood disturbance, dyspepsia or glucose intolerance. *2) Effects associated with prolonged use* (usually >12 weeks, but sometimes less) include posterior subcapsular cataracts, osteoporosis, osteonecrosis of the femoral head, myopathy and susceptibility to infection. Budesonide causes less reduction in bone mineral density than prednisolone (mean −1.04% vs −3.84% over 2 years in a randomized study of 272 patients, $p = .0084$).[57] An increased risk of post-operative sepsis with steroids has been reported in 159 patients with IBD (88 with CD, OR 3.7, 95% CI 1.2–11.0) which was not seen in patients on thiopurine therapy [OR 1.7, CI 0.7–9.6].[58] In addition, several safety cohorts indicate that steroids in combination with other immunosuppressive agents increase the risk of serious infections.[59–61] *3) Effects during withdrawal* include acute adrenal insufficiency (from sudden cessation), a syndrome of pseudo-rheumatism (with myalgia, malaise and arthralgia, similar to a recrudesence of Crohn's disease), or raised intracranial pressure. Complete steroid withdrawal is facilitated by early introduction of azathioprine, infliximab, adjuvant nutritional therapy, or timely surgery.

5.4.3.4. Monitoring. Osteoprotective therapy is considered advisable if the duration of therapy is likely to be >12 weeks, although some advocate supplements of calcium and vitamin D for all patients based on prospective trials.[62,63]

5.4.4. Anti-TNF strategies

ECCO Statement 5I
All currently available anti-TNF therapies appear to have similar efficacy and adverse-event profiles, so the choice depends on availability, route of delivery, patient preference, cost and national guidance [EL5, RG D].

ECCO Statement 5J (new)
Loss of response to anti-TNF therapy should lead to re-evaluation of disease activity, exclusion of complications and discussion of surgical options with the patient [EL5, RG D]. For active disease, reduction in interval between doses, or dose escalation are appropriate strategies before switching to another agent [EL5 RG D]. Switching is an effective strategy [EL1b, RG A], but reduces future therapeutic options. For intolerance, especially if severe, switching to an alternative anti-TNF agent is appropriate. Response to a third anti-TNF therapy occurs in some patients and may be an appropriate option [EL3 RG C], although surgical options should also be considered and discussed. Primary lack of response may be determined within 12 weeks and an alternative anti-TNF agent tried for active disease [EL3, RG C].

ECCO Statement 5K
Particular care should be taken to consider opportunistic infections as a complication of anti-TNF therapy [EL5, RG D]. Patients with fever, cough, systemic symptoms or other unexplained illness should be evaluated for opportunistic infection including tuberculosis or fungal infection, if possible with advice from an infectious diseases' specialist. The long-term combination of azathioprine/mercaptopurine and anti-TNF therapy is best avoided in young people because of the risk of hepatosplenic T-cell lymphoma [EL4, RG D].

Infliximab (Remicade®) and adalimumab (Humira®) are IgG1 anti-TNF monoclonal antibodies with potent anti-inflammatory effects, possibly dependent on apoptosis of inflammatory cells. Certolizumab Pegol (Cimzia®) is a pegylated anti-TNF Fab-antibody fragment with proven clinical efficacy despite the lack of pro-apoptotic effects. Numerous controlled trials have demonstrated efficacy of these anti-TNF agents for active Crohn's disease. Anti-TNF therapy is effective for active inflammatory CD, but should be used with care in patients with obstructive symptoms.

5.4.4.1. Efficacy as induction therapy for inflammatory CD.

5.4.4.1.1. Infliximab. A multi-centre, double-blind study in 108 patients with moderate-to-severe CD refractory to 5-ASA, corticosteroids and/or immunomodulators, demonstrated an 81% response rate at 4 weeks after 5 mg/kg infliximab compared with 17% given placebo (NNT = 1.6).[64] The duration of response varied, but 48% who had received 5 mg/kg still had a response at week 12. There was no dose response. In a large cohort from the University of Leuven, 89% of patients achieved response (defined by clinician's assessment) after induction therapy with infliximab.[65] Early treatment (top-down therapy) with infliximab has also been compared with a conventional approach (steroids +immunomodulators, step-up therapy).[18] 130 steroid-naïve patients with recent-onset CD were randomized to initial therapy with infliximab and azathioprine, or to steroids and later azathioprine. Although remission rates at 1 year were similar (77% vs 64% respectively, $p = 0.15$), 19% on step-up therapy were still on steroids, compared to 0% given top-down therapy ($p < 0.001$). Endoscopic healing was higher using the top-down approach. The SONIC study randomized 508 patients in a head-to-head, blinded, double dummy comparison of infliximab with and without azathioprine to azathioprine alone. Infliximab 5 mg/kg at 0–2 and 6 weeks and every 8 weeks thereafter with azathioprine (2.5 mg/kg) was superior to infliximab alone for the induction of steroid free remission after 26 weeks (57% vs. 45%, $p < 0.05$). Azathioprine monotherapy was the least effective therapy (30% steroid free remission after 26 weeks, $p < 0.01$ vs. both infliximab based regimens).[1] Mucosal healing (defined as the disappearance of ulcers) was higher in the combined infliximab azathiopine treatment group compared to the two other groups. In contrast preliminary data from the recent Canadian COMMIT trial showed no benefit of adding methotrexate to a combination of steroids and infliximab for the induction of clinical remission but high remission rates were achieved in both groups.[41]

Adalimumab is a fully human anti-TNF monoclonal antibody given by subcutaneous injection. In the CLASSIC I trial, 299 infliximab-naïve patients with active CD were treated with adalimumab. An induction dose of 160 mg followed by 80 mg at 2 weeks was needed to achieve remission in 36% at 4 weeks compared to 12% receiving placebo ($p < 0.05$).[66] In the GAIN trial the efficacy of adalimumab as a second line anti-TNF therapy in patients with active Crohn's disease and with loss of response or intolerance to infliximab (secondary infliximab failures) was assessed. Patiens (n = 325) were treated with adalimumab 160 and 80 mg or placebo 2 weeks apart. After 4 weeks 21% of adalimumab treated patients versus 7% of those on placebo were in clinical remission ($p < 0.001$).[67] The remission figures were lower than those in the CLASSIC I trial and suggest that a proportion of patients losing response to a first anti-TNF agent may develop a genuine resistance against this class of agents. A post-hoc analysis of the GAIN trial indicated that concomitant steroids at baseline favoured clinical remission at 4 weeks, but the exact significance of this finding in clinical practice is unclear. After the consensus, preliminary data from the open-label induction and placebo-controlled maintenance EXTEND trial exploring the efficacy of adalimumab to induce endoscopic healing indicate that, although at 12 weeks there was no benefit for endoscopic healing in the adalimumab group compared to placebo, adalimumab was significantly better at later time points up to one year at healing mucosal ulcers.[68]

5.4.4.2. Certolizumab pegol. Certolizumab pegol (certolizumab) is a pegylated anti-TNF antibody, administered by subcutaneous injection at a dose of 400 or 200 mg. In a dose finding trial, 292 patients with moderately to severely active CD received placebo, certolizumab 100, 200 or 400 mg at weeks 0, 4 and 8. At week 2 33% of patients receiving certolizumab 400 mg vs. 15% ($p = 0.01$) of those receiving placebo experienced a clinical response (defined as a CDAI decrease ≥ 100). Response rates were superior in patients with a baseline CRP ≥ 10 mg/L. Clinical remission rates at week 4 were 8% for placebo and 21% for certolizumab 400 mg.[69] In the Precise-1 trial 662 patients with moderately to severely active Crohn's disease were randomized to receive certolizumab 400 mg or placebo at weeks 0, 2 and 4 then every 4 weeks until week 24. Clinical response at week 6 was 37% for certolizumab and 26% for placebo ($p < 0.05$). Response at both weeks 6 and 26 (co-primary endpoints) was observed in 22% of patients on certolizumab and in 12% of patients on placebo ($p = 0.05$). Certolizumab was superior at inducing clinical remission at week 4 and week 26 but not at other time points. The WELCOME trial explored the efficacy of certolizumab pegol in patients with previous infliximab exposure who lost response to or became intolerant of infliximab (secondary failures).[285] A total of 539 patients received open-label certolizumab pegol at 0, 2, and 4 weeks and 329 were randomized to 400 mg every 2 or every 4 weeks through 24 weeks from baseline. After open-label induction, 39.2% of patients achieved clinical remission; remission rates on maintenance therapy were 29.2% (cerolizumab every 4 weeks) and 30.4% (cerolizumab every 2 weeks) respectively. It should be noted that although all patients in this trial were on active drug for both induction and for maintenance therapy, the study still indicates that certolizumab pegol is effective in a proportion of patients with secondary failure to infliximab. Preliminary data from the open-label MUSIC trial including 89 patients with active luminal Crohn's disease suggest that certolizumab induces endoscopic healing in patients treated up to 54 weeks. By week 10 after 4 doses of certolizumab, 40% of patients achieved endoscopic remission defined as a CDEIS score of <6 points.[70].

5.4.4.3. Adverse effects of anti-TNF therapy. Most side effects associated with anti-TNF therapy in Crohn's disease can be considered class effects and treatment with anti-TNF agents is relatively safe if used for appropriate indications. Infusion reactions with infliximab (within 2 h during or shortly after infusion) are rare and respond to slowing the infusion rate or treatment with antihistamines, paracetamol and sometimes corticosteroids.[71] Anaphylactic reactions have been reported.[72]

A delayed reaction of joint pain and stiffness, fever, myalgia and malaise may occur, especially if there has been an interval >1 year following a previous infusion. Pre-treatment with hydrocortisone is advised in these circumstances, but loss of response over time is common.[61] Infection is the main concern with the use of anti-TNF agents in Crohn's disease. Active sepsis (such as an abscess) is an absolute contraindication given the risk of overwhelming septicaemia.[72,73] Reactivation or development of tuberculosis has been reported in 24/100 000 patients with rheumatoid arthritis given anti-TNF therapy, compared to 6/100 000 not given such treatment.[74] The theoretical risk of lymphoproliferative disorders or malignancy (in view of the role of endogenous TNF in tumour suppression) has not been confirmed in post-marketing surveillance,[59,61] but follow-up is short and a recent meta-analysis of all clinical trials with anti-TNF agents in IBD suggested an increased risk of lymphoma comparable to that of thiopurines.[75] Overall, some studies report an annual mortality of up to 1%[72] and risks may be higher in the elderly.[73] However, in a recently reported large single centre cohort the risk of mortality with infliximab was not increased compared to that with non-biological therapy. Long-term combination immunosuppressive therapy (steroids, thiopurines and anti-TNF agents) increase the risk of opportunistic infections[60] and probably of hepatosplenic T-cell lymphoma. Careful patient selection and meticulous follow-up may decrease the side effect burden associated with anti-TNF therapy and with the use of immunosuppressives in general.

5.4.4.4. Summary. A recent meta-analysis of all controlled trials with anti-TNF agents indicated that adalimumab, certolizumab pegol and infliximab are efficacious for induction of remission in luminal inflammatory Crohn's disease.[76] Certolizumab pegol is only registered in Switzerland and not in the rest of Europe. Modes of administration are intravenous for infliximab, and subcutaneous for certolizumab pegol and adalimumab. The mode of delivery impacts on the frequency of drug administration and on the associated side effects. Intravenous administration can result in immediate and delayed infusion reactions (potentially severe) whereas subcutaneous injection is associated with painful injection site reactions. The route of administration is one factor that determines the choice of drug and should be discussed with the patient. In general no head-to-head comparative trials are available to guide the choice between the commercially available anti-TNF biological therapies. For infliximab, a three dose induction dosing schedule and scheduled maintenance has been shown to decrease the risk of immunogenicity and infusion reactions.[61,77] Screening for active infection and for latent tuberculosis (following national guidelines) should be performed before starting anti-TNF therapy. The potential benefits of starting anti-TNF therapy should always be balanced to the potential risks, bearing in mind that most patients will receive long-term maintenance therapy. Latent untreated or active tuberculosis, other ongoing infections, severe heart failure, a history of demyelinating disease or optic neuritis, an abdominal or perianal abscess and a history of lymphoma are contraindications to anti-TNF therapy. In patients with a history of a non-hematopoietic cancer, careful consideration should be given to initiating anti-TNF therapy. When in doubt advice from an oncologist or specialist in infectious diseases should be sought.

5.4.5. Other biological therapy

Many new biological therapies are under development.[78] The most promising novel class of agents for the treatment of Crohn's disease are selective anti-adhesion molecules. *Natalizumab* is a humanized monoclonal antibody against alpha4 integrin that inhibits leukocyte adhesion and migration into inflamed tissue. In ENACT-1, 905 patients were randomly assigned to receive 300 mg of natalizumab or placebo at weeks 0, 4, and 8.[79] The natalizumab and placebo groups had similar rates of response (56% and 49%, respectively, $p=0.05$) and remission (37% and 30%, respectively; $p=0.12$) at 10 weeks. In contrast, the ENCORE trial evaluated the efficacy of natalizumab 300 mg IV versus placebo at week 0–2–4 in 509 patients with moderately to severely active Crohn's disease and an increased baseline CRP. Clinical response was better in natalizumab patients (48% vs. 32%, $p<0.001$) as was sustained clinical remission. Of note, patients with previous exposure to infliximab responded equally well.[80] Natalizumab was much more effective as maintenance therapy although the drug is only approved for the treatment of anti-TNF refractory Crohn's disease in the USA (see Section 6.2.8). Another selective anti-adhesion molecule agent, *alicaforsen* (anti-sense oligonucleotide to human ICAM1), has not shown benefit for active Crohn's disease at the doses used in clinical trials. Efficacy data on monoclonal antibodies against interferon-γ (*Fontolizumab*),[81,82] *IL12/23 p40 (ABT-874, Ustekinumab)*[83,84] and *IL-6*[85] have been presented (for a review, see[78]). Treatment by parenteral administration of IL-10 and IL-11 is ineffective, although mucosal delivery systems are being developed.[86] The efficacy and safety of other novel approaches, such as stem cell transplantation[87] have yet to be established.

5.4.6. Thiopurines

Azathioprine (AZA) 1.5–2.5 mg/kg/day or mercaptopurine (MP) 0.75–1.5 mg/kg/day (unlicensed for use in IBD) may be used in active CD as adjunctive therapy or steroid-sparing agent. However, its slow onset of action precludes its use as a sole therapy for active disease. Purine antimetabolites inhibit ribonucleotide synthesis, but at least one mechanism of immunomodulation is to induce T-cell apoptosis by modulating cell (Rac1) signalling.[87] Azathioprine is metabolised to mercaptopurine and subsequently to 6-thioguanine nucleotides. Thioguanine is discussed in the section on maintenance therapy. Since the main role of thiopurine therapy resides in maintaining remission, dose, monitoring and side effects will be discussed in the maintenance section of this paper.

5.4.6.1. Efficacy of thiopurines to induce clinical remission. A Cochrane review of the efficacy of AZA and MP for inducing remission in active CD demonstrated a benefit for thiopurine therapy compared to placebo with an odds ratio of 2.36 (95% CI 1.57–3.53).[88] This equates to an NNT of 5 and a number needed to harm (NNH) of 14. Owing to the delayed onset of action, the response rate was higher in the studies lasting more than 16 weeks (NNT=4). In an attempt to accelerate the onset of action, a trial evaluating the efficacy of a high-dose 36 h infusion was no more effective than conventional oral dosing.[89]

5.4.7. Methotrexate

Methotrexate 25 mg/day (oral, subcutaneous or intramuscular injection — unlicensed for use in IBD) may be used in a similar fashion to thiopurines. Polyglutamated metabolites of

methotrexate inhibit dihydrofolate reductase, but this cytotoxic effect does not explain its anti-inflammatory effect and inhibition of cytokine and eicosanoid synthesis with modification of adenosine levels probably contribute more.

5.4.7.1. Efficacy of methotrexate. In a controlled study, 141 steroid-dependent patients with active CD were randomized to either 25 mg/week of intramuscular methotrexate or placebo for 16 weeks, with a concomitant daily dose of prednisolone (20 mg at initiation) that was reduced over a 3-month period. More of the methotrexate-treated group was able to withdraw steroids and enter remission compared to placebo (39% vs 19%; $p=0.025$).[90] This efficacy has been confirmed in a systematic review.[91] The same indications apply as for thiopurine therapy (see above), but at present, methotrexate is generally reserved for treatment of active or relapsing Crohn's disease in those refractory to or intolerant of thiopurines or anti-TNF agents.[92]

5.4.7.2. Dose and monitoring. Doses of <15 mg/week are ineffective for active CD, unlike rheumatoid arthritis, and 25 mg/week is the standard induction dose. The prospective controlled trials that demonstrated efficacy in Crohn's disease used an intramuscular route.[80,93] A significant reduction of drug levels and variability in the absorption of oral methotrexate as compared to subcutaneous administration has been demonstrated[94] which may explain why parenteral administration seems to be more effective.[95] However, for practical reasons relating to the reconstitution of parenteral cytotoxic drugs, oral dosing is more convenient and preferred by patients. Consequently, treatment should usually be started via the intramuscular or subcutaneous routes. A switch to oral administration may be attempted for maintenance while carefully monitoring the clinical response, although no trials are available to support this approach. Concurrent administration of folate supplementation is advisable,[92,96] although no data directly related to Crohn's disease patients are available. Measurement of full blood count and liver function tests are advisable before and within 4 weeks of starting therapy, then monthly. The same caveats as for monitoring thiopurine therapy apply. Patients should remain under specialist follow-up. Most agree that therapy can be continued for more than one year.

5.4.7.3. Adverse effects of methotrexate. Early toxicity from methotrexate is primarily gastrointestinal (nausea, vomiting, diarrhoea and stomatitis) and can be limited by co-prescription of folic acid 5 mg two or three days apart from the methotrexate. Treatment is discontinued in 10–18% of patients because of side-effects.[92] Methotrexate is contra-indicated during pregnancy and conception may best be deferred for several months after cessation of therapy. The principal long-term concerns are hepatotoxicity and pneumonitis. A study of liver biopsies in IBD patients taking methotrexate showed only mild histologic abnormalities, despite cumulative doses of up to 5410 mg.[97] Surveillance liver biopsy is not warranted, but if the AST doubles then it is sensible to withhold methotrexate until it returns to normal before a rechallenge. The prevalence of pneumonitis has been estimated to be 2–3 cases per 100 patients-years of exposure, but large series have not reported any cases.[92]

5.4.8. Other immunomodulators

5.4.8.1. Ciclosporin (CsA) and tacrolimus. The calcineurin inhibitors are of limited value in Crohn's disease. Their mechanism of action is thought to result from inhibition of the nuclear translocation of the transcription factor NFAT (nuclear factor of activated T-cells) thereby preventing downstream initiation of transcription of T-cell cytokines.

5.4.8.2. Efficacy and selection. A single trial has demonstrated some efficacy for treatment of Crohn's disease with oral CsA.[98] In that trial, 71 steroid-resistant or -intolerant patients were treated with oral CsA at a dose of 5–7.5 mg/kg/day or placebo. At the end of two months, 22 of 37 CsA treated patients (59%) improved, compared to 11 of the 34 placebo treated patients (32%) ($p=0.032$). It should be noted that the results were *response* rather than *remission*. In three further placebo-controlled trials, no efficacy of oral CsA for treatment of Crohn's disease was demonstrated.[99–101] However, three small, uncontrolled case series have reported efficacy of intravenous CsA (4–5 mg/kg/day) for both inflammatory and fistulating Crohn's disease.[102–104] There are no randomized controlled studies of intravenous CsA. Consequently oral CsA for steroid-refractory or steroid-dependent Crohn's disease cannot be recommended, but the use of short term intravenous CsA to induce remission is still debated.

In contrast, oral tacrolimus for inflammatory Crohn's disease has only been reported in uncontrolled studies or case reports. These reported short and long-term therapeutic advantage for steroid-refractory or -depedent patients.[105–107] The limited experience with tacrolimus is insufficient to recommend its general use for therapy of inflammatory luminal Crohn's disease.

5.4.9. Nutritional therapy

5.4.9.1. Efficacy of nutritional therapy. There have been no placebo-controlled trials of nutritional therapy for active CD in adult patients. However, elemental or polymeric diets appear less effective than corticosteroids. In a Cochrane systematic review, the four rigorously controlled trials comparing enteral therapy (in 130 patients) with prednisolone (in 123 patients) showed steroids to be more effective (OR 0.3, 95% CI 0.17–0.52).[26,108] The number needed to treat was 4. There was no difference in efficacy between elemental and polymeric diets. A distinction must be drawn between primary therapy to induce remission and adjunctive therapy to support nutrition.

5.4.9.2. Summary. Unlike in the management of paediatric/adolescent Crohn's disease, enteral therapy is regarded as only appropriate for adjunctive treatment to support nutrition and not for primary therapy. It is generally considered appropriate to induce remission only for patients who decline other drug therapy. It is not recommended for steroid-refractory, or steroid-dependent disease. However, it is important not to underestimate the role of nutrition as supportive care in patients with Crohn's disease, even if there is limited evidence to support its use as a primary therapy to induce remission.[109] Total parenteral nutrition is appropriate adjunctive therapy in complex, fistulating disease.

6.0. Management of medically induced remission

6.1. Medical management of patients in medically induced remission

6.1.1. General recommendations

In view of the adverse effects of cigarette smoking on the course of Crohn's disease, smoking should be discouraged in all patients. Data from observational studies show that smoking increases the need for steroids, immunosuppressants and operations. Conversely, smoking cessation may improve the course of the disease[110–112] [EL2b]. Active programs of smoking addiction should be recommended.

The absolute requirement and choice of medication for prevention of relapse in patients with medically induced remission should take into account three main factors: the course of the disease (initial presentation, frequency, and severity of flares); the extent of disease (localised or extensive — see Sections 1.112 and 1.1.13); and the effectiveness and tolerance of treatments previously used for induction of remission or maintenance. Other factors such as the presence of biological or endoscopic signs of inflammation and the potential for complications should also be considered. In addition, there may be other constraints (logistic, social, or financial) that impact on treatment choices. Finally, patients should be encouraged to participate to the decision-making process.

Patients in remission should be clinically assessed on a regular basis. Although monitoring of the C-reactive protein is frequently performed, the consequences for adjusting treatment remain unclear. Some also recommend imaging or endoscopy, but repetition of these procedures is not recommended routinely, but only in specific situations.

6.1.2. First presentation of localised disease

ECCO Statement 6A
After the first presentation if remission has been achieved with systemic steroids, a thiopurine [EL1a, RG A] or methotrexate [EL1b, RG A] should be considered. There is no consistent evidence for efficacy of oral 5-aminosalicylic acid [EL1b, RG B]. No maintenance treatment is an option for some patients [EL5 RG D].

There is no evidence that mesalazine is useful for maintaining medically induced remission, as the results of meta-analysis are inconsistent (see Section 6.2.1). Some consider that no maintenance treatment is an option after the first flare. Taking into account the high risk of relapse and of steroid dependence, and the higher success rate when introduced early, azathioprine is favoured if remission has been achieved with systemic steroids (see Section 6.2.4). Mercaptopurine (1–1.5 mg/kg/day) can be tried in patients intolerant of azathioprine (except in cases of pancreatitis and cytopenia).[113] Methotrexate is an alternative, especially for patients intolerant of thiopurines (Section 6.2.5).

6.1.3. Relapse of localised disease

ECCO Statement 6B
If a patient has a relapse, escalation of the maintenance treatment can be considered [EL5, RG D]. Steroids should not be used to maintain remission [EL1a, RG A]. Surgery should always be considered as an option in localised disease [EL4, RG D].

If a relapse occurs, azathioprine should be considered (see Section 6.2.4). Corticosteroids (including budesonide) are not effective for maintenance of remission, and the long-term use of corticosteroids is associated with unacceptable side effects, especially osteoporosis. Budesonide increases the time to relapse but is not effective at maintaining remission for 1 year; bone loss is less, but not eliminated (see Section 6.2.3).

6.1.4. Extensive disease

ECCO Statement 6C
For patients with extensive disease, azathioprine is recommended for maintenance of remission [E1b, RG A].

Taking into account the risks of relapse and the higher success rate when introduced early, azathioprine is recommended in patients with extensive Crohn's disease (see Section 6.2.4)

6.1.5. Steroid-dependent Crohn's disease

ECCO Statement 6D
Patients who are dependent on corticosteroids should be treated with thiopurines or methotrexate with or without anti-TNF therapy [EL1a, RG A for thiopurines and methotrexate], EL1a, RG B for infliximab and adalimumab], although surgical options should also be considered and discussed.

Immunomodulators (azathioprine/mercaptopurine, methotrexate) are effective in steroid-dependent Crohn's disease (NNT 3).[14,93] Ileal resection is an alternative for those with localised disease depending on other disease characteristics (see Surgery for Crohn's disease Section). A very effective approach to spare steroids is the early introduction of anti-TNF agents. Selection of patients appropriate for biological therapy depends on clinical characteristics and previous response to other medical therapies. Steroid-dependent patients may derive greater benefit from the early introduction of biological therapy.[17] However, a study of 133 patients with active Crohn's disease who had not previously received glucocorticoids, antimetabolites, or infliximab also suggested benefit of early

biological therapy in this relatively treatment naïve group. This trial randomized patients to either early combined immunosuppression or conventional treatment (commonly referred to as the Step Up/Top Down study).[18] At week 52, 61.5% of patients in the combined immunosuppression group were in remission without corticosteroids and without surgical resection compared with 42.2% in the control group (absolute difference 19.3%, 95% CI 2.4–36.3, $p=0.028$). It has now been established (through the SONIC study) that combination treatment with infliximab and azathioprine is more effective than infliximab alone for maintaining steroid-free remission in patients at an early stage of disease.[1]

6.1.5. Relapse while on azathioprine

ECCO Statement 6E
Patients receiving azathioprine or mercaptopurine who relapse should be evaluated for adherence to therapy and have their dose optimised. Change of their maintenance therapy to methotrexate [EL1b RG B] or anti-TNF therapy [EL1a RGB] should be considered. Surgery should always be considered as an option in localised disease [EL4, RG D].

Patients receiving azathioprine or mercaptopurine who relapse whilst on standard maintenance doses can have their dose escalated (>2.5 mg/kg/day or >1.5 mg/kg respectively) until leucopenia occurs [EL3, RG D], or according to 6-TGN concentrations [EL2a, RG B] (see Section 5.4.6). Methotrexate is another option [EL1b, RG B] (see Section 6.2.5). Anti-TNF therapy has also proven to be effective in this setting [EL1a, RGA] (see Section 6.2.7).

6.1.6. Maintenance after induction of remission with Anti-TNF therapy

ECCO Statement 6F
If remission has been achieved with an anti-TNF agent, maintenance with regular anti-TNF therapy should be considered [EL1b, RG B]. Azathioprine may be considered in combination with anti-TNF therapy or is an option as monotherapy if naïve to thiopurines [EL2b, RG C].

Patients in a scheduled-treatment strategy with regular infliximab, appear to fare better for many (but not all) clinical endpoints, compared to patients in an episodic (on-demand) strategy [EL1b]. Concomitant immunosuppressant therapy (thiopurines, methotrexate) with anti-TNF agents is not associated with better clinical efficacy in patients who have already failed these drugs [EL1b]. However, combination of infliximab plus azathioprine is of greater efficacy in achieving and maintaining steroid-free remission than infliximab monotherapy or azathioprine monotherapy in patients naïve to both therapies [EL1b] (see Section 6.2.7).

6.1.7. Duration of maintenance treatment

ECCO Statement 6G
For patients in remission on azathioprine as maintenance treatment, cessation may be considered after four years of remission [EL2b, RG C]. Benefit and risks of continuing azathioprine should be discussed with individual patients.

A double-blind placebo-controlled non-inferiority study comparing azathioprine withdrawal with its continuation in patients on azathioprine for more than >3.5 years found that the rates of relapse after 18 months were 21% and 8%, respectively[117] (see Section 6.2.4). The hypothesis that azathioprine was inferior to placebo was not rejected. Long-term evaluation of these patients has been recently reported.[118] The median follow-up time after azathioprine interruption was 54 months; 32 of 66 patients had a relapse. The cumulative probabilities of relapse at 1, 3, and 5 years were 14%, 53% and 63%. Among the 32 relapsing patients, 23 were retreated by AZA alone, all but 1 achieved successful remission. Thiopurine therapy has been associated with an increased risk of non-Hodgkin's lymphoma. [119,120] Lewis et al. [121] conducted a decision analysis study using a Markov model. They concluded that azathioprine results in increased quality-adjusted life expectancy, especially in young patients who have the lowest baseline risk of lymphoma and the greatest life expectancy in the absence of Crohn's disease related death. The benefits of treatment exceed an increase in lymphoma risk postulated by the most extreme studies.

ECCO Statement 6H
No recommendation can be given for the duration of treatment with methotrexate or anti-TNF agents, although prolonged use of these medications may be considered if needed [EL3, RG C]. Potential risks and benefits should be discussed on an individual basis.

Long-term follow-up of Crohn's disease patients taking methotrexate does not demonstrate an increase risk of severe hepatotoxicity, as previously suggested in other diseases.[97] In two series, methotrexate withdrawal in patients maintained for several years with this drug was associated with a high proportion of relapse.[121,122]

The benefit of continuing an immunosuppressant such as azathioprine or methotrexate in combination with anti-TNF is discussed in Section 6.2.7. The question of whether treatment with anti-TNF agents can be safely interrupted after a period of prolonged remission is of great interest to patients and physicians. Recently, interim results of a prospective study conducted to assess the risk of relapse after infliximab discontinuation in patients on combined maintenance with immunosuppressant therapy were presented.[123] 115 patients with luminal Crohn's disease treated

for at least one year with scheduled infliximab combined with azathioprine or methotrexate and in stable remission without steroids for at least 6 months were prospectively recruited into the study. Infliximab therapy was withdrawn, and after the last infusion immunosuppressant therapy was kept at a stable dose. After a median follow-up time of 12 months, 45 relapses were observed. A subgroup of patients with very low risk of relapse could be identified through a combination of biological and endoscopic markers. In relapsing patients, infliximab re-treatment was well tolerated and induced remission.

6.2. Specific considerations on medications for maintenance of medically induced remission

Details of the action, pharmacology, dosage, side effects and monitoring of aminosalicylates, steroids, thiopurines, methotrexate and anti-TNF therapy are in the Active Disease section.

6.2.1. Aminosalicylates

6.2.1.1. Evidence. Randomized trials designed to evaluate the efficacy of aminosalicylates (5-ASA) for maintaining medically induced remission are shown in Table 6.1.[124–134] No additional study to evaluate the efficacy of 5-ASA for this indication has been published in Crohn's disease since 2001. The five meta-analyses carried out from these trials are summarized in Table 6.2.[135–139] The first meta-analysis by Steinhart et al. [135] shows a benefit of mesalazine (OR 0.63; CI 0.50–0.79), but not of sulfasalazine (OR 1.08; CI 0.81–1.34). The meta-analysis by Messori et al.[136] also shows a benefit of mesalazine, which was associated with a reduction in the risk of clinical relapse between 0 and 6 months (OR 0.56; CI 0.37–0.84; $p<0.01$) and between 6 and 12 months (OR 0.47; CI 0.33–0.67; $p<0.001$). The meta-analysis by Camma et al.[137] is more complete, but also includes 5 studies designed for post-operative prevention among the 15 studies analysed. A significant reduction in the relapse risk was found when all patients were included (difference between 5-ASA and placebo: −6.3%; CI −10.4% to −2.1%), but this reduction was not significant when patients treated for medically induced remission alone were considered. No dose response could be demonstrated. When the four trials with poor quality scores were excluded, no benefit from aminosalicylates was found.

A Cochrane Database systematic review on mesalazine for maintenance of medically induced remission in Crohn's disease has been published by Akobeng et al in 2005.[138] The odds ratio for 6 studies where participants were followed up for 12 months was 1.00 (95% CI 0.80–1.24). For the seventh study where follow-up was for 24 months,[96] the odds ratio was 0.98 (95% CI 0.51–1.90). When only participants who completed the study were analysed, the odds ratio (fixed effects model) for the six 12-month studies was 0.74 (95% CI 0.57–0.96), but using the random effects model, the OR was 0.68 (95% CI 0.45–1.02). The OR for the seventh study where follow-up was for 24 months,[96] was 0.86; 95% CI, 0.42 to 1.78. In 2007, Steinhart et al.[139] published a review including a meta-analysis of 9 RCTs that investigated mesalazine for maintenance of medically induced remission in order to explore the possibility that variations in delivery of different 5-ASA formulations may explain the inconsistent results seen in the published meta-analyses. Compared to the Cochrane Database review by Akobeng et al.[138] they excluded the study by Mahmud et al.[134] which investigates olsalazine vs placebo, but added three studies excluded by Akobeng et al.[138] because the duration of follow-up was <6 months[126] or because patients were randomized during a flare.[126,131] They found a clinically significant therapeutic advantage for treatment with mesalazine over control [OR=0.70 (95% CI 0.52–0.93; $p=0.01$], with a benefit of 6.6% (39.1 vs 32.5%) and an NNT of 16. Treatment

Table 6.1 Placebo-controlled trials of mesalazine for maintenance of medically induced remission in Crohn's disease.

Author [ref.]	Year	Number of patients	Dosage (g/j)	Duration (months)	Relapse rate (%)			Comment
					5-ASA	Placebo	*P*	
IMSG[124]	1990	248	1.5	12	8	31	0.053	
Bresci[125]	1991	38	1.6	36	80	94	NS	Not strictly randomized
Brignola[126]	1992	44	2	4	52	59	NS	
Prantera[127]	1992	125	2.4	12	34	55	0.02	
Gendre[128]	1993	161	2	24	47	42	NS	Low risk
					55	71	<0.003	High risk [a]
Arber[129]	1995	59	1	12	27	55	< 0.05	
Thomson[130]	1995	286	3	12	27	31	NS	I+C
					40	26	NS	I
Modigliani[131]	1996	129	4	12	62	64	0.05*	*For steroid weaning
De Franchis[132]	1997	117	3	12	58	52	NS	
Sutherland[133]	1997	293	3	11.5	25	36	NS	I+C
					21	41	0.02	
Mahmud[134]	2001	328	2	12	48	45	NS	Olsalazine compared to placebo in ileocolonic Crohn's disease

IMSG: International Mesalazine Study Group. I: ileal C: colonic.
[a] Remission <3 months.

Table 6.2 Meta-analysis of placebo-controlled trials of mesalazine for maintenance of medically induced remission in Crohn's disease.

Author [ref.]	Year	Number of trials	Number of patients	Duration (months)	Result		
					Odds ratio	$IC_{95\%}$	*p*
Steinhart[135]	1994	10	1022	12	0.77	0.64–0.92	–
Messori[136]	1994	8	941	12	0.47	0.33–0.67	<0.001
Camma[137]	1997	10	1371	4 – 48	–	–	0.06
Akobeng[138]	2005	7	1500	12–24	1.00	0.80–1.24	ns
Steinhart[139]	2007	9	1305	4–24	0.70	0.52–0.93	0.01

with pH 7-dependent mesalazine significantly reduced the risk of relapse (OR 0.38; 95% CI 0.17–0.85; $p=0.01$) but not treatment with controlled-release mesalazine and pH 6-dependent mesalazine. The NNT to maintain medically induced remission for pH 7-dependent mesalazine was 5. They suggest that the mesalazine formulation may be a contributory factor in the results of RCT in patients maintained on mesalazine.

6.2.1.2. Summary. For maintenance of medically induced remission in Crohn's disease, the efficacy of mesalazine remains controversial, due to inconsistent results seen in the published meta-analyses [EL1b]. The effectiveness of sulfasalazine or of olsalazine is not established [EL1b]. 5-ASA are not recommended for maintenance of medically induced remission in Crohn's disease.

6.2.2. Antibiotics

6.2.2.1. Evidence. The results of clinical trials are summarized in Table 6.3.[54,140–146] Most are related to anti-mycobacterial agents, but these antibiotics are also potentially active against intestinal bacteria. A meta-analysis of anti-mycobacterial therapy[147] includes six fully published studies. Patients in two trials[144,145] whose remission was induced by a combination of antibiotics and steroids benefited (OR 3.37; CI 1.38–8.24, whereas patients on a combination of antibiotics compared to conventional therapy[141–143,146] did not (OR 0.69; CI 0.39–1.21). A large Australian study published in 2007 confirms this[54]: 213 patients were randomized to clarithromycin 750 mg/day, rifabutin 450 mg/day, clofazimine 50 mg/day or placebo, in addition to a 16-week tapering course of prednisolone. Those in remission at week 16 continued their study medications in the maintenance phase of the trial. At week 16, there were significantly more subjects in remission in the antibiotic arm (66%) than the placebo arm (50%; $p=0.02$). Of 122 subjects entering the maintenance phase, 39% taking antibiotics experienced at least 1 relapse between weeks 16 and 52, compared with 56% taking placebo ($p=0.054$). At week 104, the figures were 26% and 43%, respectively ($p=0.14$). During the following year, 59% of the antibiotic group and 50% of the placebo group relapsed.

6.2.2.2. Summary. Evidence for the effectiveness of antibiotics, in particular of anti-mycobacterial agents, for the maintenance of medically induced remission is lacking [EL1b].

6.2.3. Corticosteroids

6.2.3.1. Evidence. A meta-analysis of classic corticosteroids such as prednisolone retained 3 out of 8 studies identified in the literature, including 403 patients. The population was heterogeneous: patients had medically- or surgically-induced

Table 6.3 Placebo-controlled trials of antibiotics for maintenance of medically induced remission in Crohn's disease.

Author [ref.]	Year	Number of patients	Antibiotics	Duration (months)	Relapse rate (%)			Concomitant therapy
					Antibiotics	Placebo	*P*	
Elliott[140]	1982	51	Sulfadoxine+Pyrimethamine	12	62	50		No
Shaffer[141]	1984	27	Ethambutol+Rifampicine	24	64	36	NS	Steroids Sulfasalazine
Basilisco[142]	1989	24	Rifabutine	6	71	62		Miscallenaous
Afdhal[143]	1991	49	Clofazimine	12	36	50		Steroids
Prantera[144]	1994	40	Ethambutol+Clofazimine+ Dapsone+ifampicine	9	89	41	0.03	Steroids
Swift[145]	1994	126	Ethambutol+Rifampicine+ Isoniazide	24	65	62	NS	Steroids Mesalazine
Goodgame[146]	2001	31	Clarithromycine+Ethambutol (3 months)	12	–	–	NS	No
Selby[54]	2007	213 [a]	Clarithromycine+Rifabutin+ clofazimine	24	26	43	NS	Steroids for induction

[a] Of 213 included in the study, 122 patients entered in the maintenance phase.

Table 6.4 Placebo-controlled trials of budesonide for maintenance of medically induced remission in Crohn's disease.

Author [ref.]	Year	No. of patients	Dosage (mg/day)	Duration (months)	Relapse rate (%)			Formulation	Comment
					Budesonide	Placebo	*p*		
Löfberg[148]	1996	90[a]	6	12	74	63	NS	Controlled ileal release	After induction with either prednisolone or budesonide
			3		59				
Greenberg[149]	1996	105[a]	6	12	61	67	NS	Controlled ileal release	After induction with budesonide in a RCT
			3		70				
Ferguson[150]	1998	75[a]	6	12	46	60	NS	Controlled ileal release	After induction with budesonide in a RCT
			3		48				
Gross[151]	1998	179	3	12	67	65	NS	pH-modified release	After induction with 6-methylprednisolone
Cortot[152]	2001	120[a]	6	4–5	33	65	0.05 at 3 months	Controlled ileal release	Steroid-dependent patients receiving 10–30 mg predniso(lo)ne at entry
Hanauer[153]	2005	110[a]	6	12	40	47	NS	Controlled ileal release	After induction with budesonide in a RCT

[a] Inclusion restricted to patients with ileal or proximal colonic involvement.

remission and had or had not been treated with corticosteroids before. No significant difference was found between steroids and placebo after 6, 12 or 24 months.[56]

The six randomized placebo-controlled clinical trials evaluating budesonide in ileocolic Crohn's disease for maintenance of medically induced remission are shown in Table 6.4.[147–153] One study compared budesonide to 5-aminosalicylates,[154] one compared budesonide to low-dose traditional systemic corticosteroids,[155] one compared two doses of budesonide with no control group[156] and an additional trial compared administration of a fixed dose of budesonide (6 mg daily) with a flexible dose (3–9 mg).[157] Four meta-analyses have been published.[158–161] In the first,[158] 4 trials (449 patients) comparing the effectiveness of budesonide 3 mg ($n=174$) or 6 mg ($n=90$) to placebo ($n=185$) were considered.[148–150] The one year relapse rates were 66%, 58% and 64% respectively (OR −0.8%; CI −9.9 to +8.3%; $p=0.42$). The frequency of corticosteroid side effects was similar between budesonide and placebo, but significant heterogeneity was noted, with two trials reporting lower rates of side effects. In the second,[159] three trials were taken into account,[148–150] since the fourth[151] had used a different form of budesonide, and the conclusion was identical. In a further meta-analysis,[160] four RCTs with identical protocols, including the Hanauer study,[153] were pooled. A total of 380 patients with Crohn's in medically induced remission were randomized to receive oral budesonide 3 mg, 6 mg, or placebo daily for 12 months. Budesonide was not effective at maintaining remission for 12 months, but the median time to relapse was 268, 170, and 154 days for budesonide 6 mg, budesonide 3 mg, and placebo groups, respectively ($p=0.007$). A Cochrane Database systematic review on budesonide for maintenance of surgically- or medically induced remission in Crohn's disease has been published by Benchimol et al. in 2009, after the Consensus.[161] Eleven studies were included in the review, including 8 studies comparing budesonide with placebo, and the 6 studies in patients with medically induced remission. Budesonide 6 mg daily was no more effective than placebo for maintenance of remission at 3 months (RR 1.25; 95% CI 1.00 to 1.58; $p=0.05$), 6 months (RR 1.15; 95% CI 0.95 to 1.39; $p=0.14$), or 12 months (RR 1.13; 95% CI 0.94 to 1.35; $p=0.19$). Budesonide was not more effective than weaning doses of prednisolone for maintenance of remission at 12 months (RR 0.79; 95% CI 0.55 to 1.13; $p=0.20$), but was better than mesalamine 3 g/day (RR 2.51; 95% CI 1.03 to 6.12; $p=0.04$). No differences in efficacy were detected based on the different formulations of budesonide, surgically or medically induced remission, or budesonide dose. The use of budesonide 6 mg resulted in slight improvements in mean time to relapse (weighted mean difference 59.93 days; 95% CI 19.02 to 100.84; $p=0.004$). Adverse events were more frequent in patients treated with 6 mg of budesonide compared with placebo but these events were relatively minor and did not result in increased rates of study withdrawal. Cortot et al.[152] evaluated the possibility of switching from systemic steroids to budesonide CIR in prednisolone/prednisone dependent patients with inactive Crohn's disease affecting the ileum and/or ascending colon. After 13 weeks without predniso(lo)ne, relapse rate was 32% in the budesonide group, and 65% in the placebo group ($p<0.001$). The number of glucocorticosteroid side effects was reduced by 50% by switching from prednisolone and was similar in the budesonide and placebo groups. Schoon et al.[57] found a significant benefit for budesonide over prednisolone when assessing bone mineral density. However, in a longitudinal study of budesonide, prednisone and nonsteroid therapy, Cino et al. found that budesonide does not confer a benefit over low-dose prednisone for the preservation of bone mineral density.[162] Abnormal adrenocorticoid stimulation tests were seen more frequently in patients receiving both 6 mg and 3 mg daily compared with placebo. The authors concluded that the modest benefits in terms of lower CDAI scores and longer time to relapse are offset by higher treatment-related adverse event rates.

6.2.3.2. Summary. Corticosteroids are not effective for maintenance of medically induced remission in Crohn's disease [EL1a]. Budesonide may delay relapse after medically induced remission, but is not effective at maintaining remission for 12 months [EL1a]. Budesonide can replace

Table 6.5 Placebo-controlled trials of azathioprine (AZA) or mercaptopurine (MP) for maintenance of medically induced remission in Crohn's disease.

Author [ref.]	Year	Nb of patients	Drug (mg/kg/day)	Duration (months)	Relapse rate (%)			Randomized patients
					AZA	Placebo	*p* or 6-MP	
Willoughby[164]	1971	10	AZA (2.0)	6	20	60	<0.05	Steroid-dependent patients
Rosenberg[165]	1975	20	AZA (2.0)	9	20	50	<0.01	Steroid-dependent patients
O'Donoghue[166]	1978	51	AZA (2.0)	12	5	41	<0.05	Patients in remission on azathioprine (withdrawal study)
Summers[23] (NCCDS) (part I, phase 2)	1979	19	AZA (2.5)	9	16	25	NS	Patients who achieved remission after 17 weeks
Summers[23] (NCCDS) (part II)		151	AZA (1.0)	24	–	–	NS	Patients with inactive disease
Candy[114]	1995	63	AZA (2.5)	12	58	93	<0.001	Patients with active disease. Induction of remission with a 3-month course of prednisone
Markowitz[168]	2000	55	MP (1.5)	18	9	47	0.007	Children with newly diagnosed Crohn's disease; induction with prednisone
Lémann[117] (GETAID)	2005	83	AZA (1.7)	18	8	21	NS (non-inferiority design)	Patients in remission on azathioprine >42 months (withdrawal study)

predniso(lo)ne in steroid dependent patients to improve tolerability [EL1b].[163] Corticosteroids including budesonide are not recommended for maintenance of medically induced remission in Crohn's disease.

6.2.4. Thiopurines

6.2.4.1. Evidence. Clinical trials evaluating the efficacy of azathioprine for maintenance of medically induced remission in Crohn's disease are listed in Table 6.5.[23,114,117,164–168] Mercaptopurine (1–1.5 mg/kg/day) which, like azathioprine in many countries except France, is unlicensed for Crohn's disease, and is considered equivalent to azathioprine. No additional placebo-controlled study has been reported in medically induced remission since 2005, albeit three trials evaluating the efficacy of azathioprine or mercaptopurine to prevent recurrence after surgery were recently published (see Section 3, Chapter 8.0). Two studies[164,165] entered steroid dependent patients and attempted to withdraw steroids after adding azathioprine or placebo. Two other studies[117,166] identified groups of patients who were in remission on azathioprine and randomized patients to receive a one year[166] or 18 month course of either azathioprine or placebo[117].Three meta-analyses of these studies have been published by the same group, including two Cochrane Database systematic reviews.[169–171] The more recent publication[171] analysed six clinical trials, including 530 patients treated with azathioprine (n=231) or placebo (n=299) for medically induced remission. The Markowitz's study[168] is not included in the review, presumably because it was conducted in children who were not quiescent at entry in the trial, and the study drug was mercaptopurine. The overall remission rate was 71% (95% CI 64% to 77%) for azathioprine and 52% (95% CI 36% to 66%) for placebo (OR 2.32; CI 1.55–3.49; NNT to prevent one relapse=6). There was a dose–response effect (OR1.20; CI 0.60–2.41 at 1 mg/kg/day; OR 3.01; CI 1.66–5.45 at 2 mg/kg/day; and OR 4.13; CI 1.59–10.71 for 2.5 mg/kg/day). Two clinical trials have examined the steroid-sparing effect of thiopurines,[164,165] which was observed in 87% of patients in the azathioprine group and 53% on placebo (OR 5.22; CI 1.06–25.68). However, the risk of premature withdrawal from the study for side effects was significantly increased with azathioprine compared to placebo (OR 3.74; CI 1.48–9.45).

In three recent studies,[1,116,170] azathioprine was used as a comparator to evaluate the efficacy of infliximab alone,[1] infliximab combined with azathioprine,[1,116] or everolimus[170] to induce and maintain remission. Patients initially received steroids until response which were then tapered. Steroid-free remission (CDAI<150) was the primary endpoint of the three trials. In the azathioprine groups, success rates were remarkably similar: 29% at 6 months,[116] 30% at 6 months[1] and 38% at 7 months.[170] The apparent discrepancy between these findings and previous evidence suggesting a more pronounced beneficial effect of azathioprine on the maintenance of remission may be the more stringent criterion for success which was used in these recent studies. Another explanation could be the selection of patients with a more advanced disease, although in the study by Colombel et al.[1] the median disease duration was 2 years. In the Markowitz's study,[168] children were enrolled before receiving any treatment, after two less than 2 weeks of unsuccessful treatment with 5-ASA or if they had received less than 6 weeks of prednisone. Fifty-five children were randomized to treatment with mercaptopurine or placebo within 8 weeks of initial diagnosis. Both groups also received prednisone. Although remission was induced in 89% of both groups, only 9% of the remitters in the 6-MP group relapsed within the 18 months following randomization, compared with 47% of

controls ($p=0.007$). D'Haens et al.[18] recently published a study comparing two strategies in patients who had been diagnosed with Crohn's disease within the past 4 years (median, 2 weeks from diagnosis) and who had not previously received corticosteroids, antimetabolites, or biological agents. They randomly assigned 133 patients to either early combined immunosuppression (infliximab 5 mg/kg at weeks 0, 2, and 6, with azathioprine and additional treatment with infliximab and, if necessary, corticosteroids) or conventional management (corticosteroids, followed, in sequence, by corticosteroids+azathioprine in patients who experienced a relapse, and infliximab if necessary). At week 26, 39 (60%) of 65 patients in the combined immunosuppression group were in steroid free remission without surgical resection, compared with 23 (36%) of 64 controls ($p=0.0062$). Corresponding rates at week 52 were 40/65 (61%) and 27/64 (42%) ($p=0.0278$). These two studies suggest that early introduction of azathioprine combined with steroids (or infliximab) within the months following diagnosis can improve success rate.

T(h)ioguanine, the active metabolite of azathioprine and mercaptopurine, might be an alternative to these agents in intolerant patients. No controlled study is available, but in several series thioguanine appeared to be similarly effective to azathioprine or mercaptopurine.[173,174] Unfortunately, a high frequency of liver abnormalities has been reported, mostly nodular regenerative hyperplasia[172–177] which is an irreversible cause of portal hypertension. Therefore, thioguanine cannot currently be recommended for maintenance of Crohn's disease.

6.2.4.2. Summary. These data show that azathioprine (2–2.5 mg/kg/day) is effective for the maintenance of remission in Crohn's disease [EL1a]A steroid-sparing effect has been shown [EL1a]. Studies suggest that early introduction of azathioprine can improve success rate [EL1b]. No specific study has been conducted for maintenance of medically induced remission with mercaptopurine but this drug, used at a lower dose (1–1.5 mg/kg/day), is considered equivalent to azathioprine [EL1b].

6.2.5. Methotrexate

6.2.5.1. Evidence. Two placebo-controlled trials evaluating the effectiveness of methotrexate for maintenance of medically induced remission have been published.[93,178] The earlier study included only 28 patients and compared oral methotrexate 15 mg/week to placebo over 1 year. Relapse rates were 43% and 80% respectively, but because of frequent adverse events, only 31% were in remission taking methotrexate at the end of the study.[178] A larger study included 76 patients who had achieved remission on intramuscular methotrexate (25 mg/week). Patients were randomly allocated to continue intramuscular methotrexate (15 mg/week) or placebo.[93] After 40 weeks, remission rates were 65% and 39% ($p=0.04$) respectively. Among the 36 patients who had a relapse, 22 were then treated with open-label methotrexate 25 mg/week and 55% achieved remission. There are no controlled studies over longer periods, but results of several open studies suggest a certain loss of efficacy of methotrexate treatment with time.[121,122] No study is available comparing azathioprine and methotrexate for maintenance of remission.

6.2.5.2. Summary. These data indicate that intramuscular methotrexate (15 mg/week) is effective for maintenance of remission in Crohn's disease, at least in patients of whom remission has been achieved with this agent [EL1b].

6.2.6. Other immunosuppressants

6.2.6.1. Evidence. Two placebo-controlled trials failed to show any benefit from oral ciclosporin 5 mg/kg/day given for 3 to 18 months to induce and maintain remission.[99,101] No controlled studies are available for maintenance of remission by mycophenolate mofetil, tacrolimus, or cyclophosphamide.

6.2.6.2. Summary. Evidence for the effectiveness of ciclosporin [EL1b], mycophenolate mofetil, tacrolimus and cyclophosphamide [EL3b] for the maintenance of remission in Crohn's disease is currently lacking.

6.2.7. Anti-TNF agents

6.2.7.1. Evidence. Clinical trials evaluating the efficacy of anti-TNF agents for maintenance of medically induced remission in luminal Crohn's disease are listed in Table 6.6[1,28,115,179,184] (for fistulating Crohn's disease — see Chapter 9.0).

Two meta-analyses of these studies have been recently published, including a Cochrane Database Systematic Review[76,185] published after the Consensus. In the first,[76] because of heterogeneity, two different types of study design were analysed separately: long-term (20–52 weeks) maintenance trials with randomization of responding patients to infliximab ($n=2$), adalimumab ($n=1$) or certolizumab ($n=1$) at weeks 2–6 after open-label induction, and long-term (24–28 weeks) induction trials with randomization before induction ($n=3$). In overall analysis, among responders after open-label induction, anti-TNF therapy was more effective than the placebo for maintenance of remission at weeks 20–30 and 48–52 (mean difference, 23%; 95% CI, 18%–29%; $P<0.001$). When considering responders and nonresponders after open-label induction in 3 trials, mean difference and 95% CI were 11.6% and 5%–18%, respectively, at weeks 20–30. Three short- and long-term induction/maintenance trials evaluating certolizumab ($n=1$) and CDP571 ($n=2$) were pooled. In overall analysis, anti-TNF therapy was more effective than the placebo for maintenance of remission at weeks 20–30 but in subgroup analysis, CDP571 was not effective in maintaining remission. In the 21 studies enrolling 5356 individuals included in the meta-analysis, anti-TNF therapy did not increase the risk of death, malignancy, or serious infection.

In the Cochrane Database review,[185] the authors did not combine the data from trials involving different anti-TNF agents. One study evaluating certolizumab pegol[28] was excluded because it reported combined induction and maintenance data, and the authors of the review felt it was not possible to evaluate maintenance therapy in clinical responders based on the published data. In the pooled analysis, infliximab was found to be superior to placebo for the maintenance of remission (RR 2.50; 95% CI 1.64 to 3.80;

Table 6.6 Randomized controlled trials of anti-TNFα including infliximab (IFX), adalimumab (ADA), certolizumab (CTZ) and CDP571 for maintenance of medically induced remission in luminal Crohn's disease.

Author [ref.]	Year	Nb of randomized patients (initial population)	Anti-TNF	Duration (weeks)	Clinical remission rate (%)			Randomized patients
					Anti-TNF	Placebo	*p*	
Rutgeerts[180]	1999	73 (73)	IFX 10 mg/kg/8 weeks	44	53 [a]	20 [a]	0.013	Responders to an initial IFX treatment
Sandborn[179]	2001	169 (169)	CDP571 10 mg/kg/8 weeks 10 mg/kg/12 weeks	24	11 11	4 3	– –	Patients with active disease randomized to CDP571 10 mg/Kg or 20 mg/Kg or placebo and then continued maintenance
Hanauer[115] (ACCENT 1)	2002	335 (573)	IFX 5 mg/kg/8 weeks 10 mg/kg/8 weeks	54	28 [a] 38 [a]	14 [a]	0.007 $p<0.001$	Responders at week 2 to open-label IFX (single infusion of 5 mg/Kg)
Sandborn[181]	2004	396 (396)	CDP571 10 mg/kg	28	24	20	NS	Patients with active disease (induction and maintenance)
Feagan[183]	2005	271	CDP571 10 mg/kg/8 weeks	36	29 [b]	37 [b]	NS	Steroid-dependent patients (in remission at entry)
Colombel[27] (CHARM)	2007	499 (854)	ADA 40 mg eow 40 mg/week	56	36 41	12	<0.001	Responders to open-label ADA (80 mg/40 mg) at week 4
Sandborn[184] (CLASSIC 2)	2007	55 (276)	ADA 40 mg eow 40 mg/week	56	79 83	44	<0.05	Patients from an induction RCT then received open-label ADA 40 mg at week 0 and 2. Remitters at week 4 enrolled
Schreiber[182] (PRECISE 2)	2007	428 (668)	CTZ 400 mg/4 weeks	26	48	29	<0.001	Responders to open-label induction with CTZ 400 mg at weeks 0, 2, 4
Sandborn[28] (PRECISE 1)	2007	662 (662)	CTZ 400 mg/4 weeks	26	10	14	0.07	Patients with active disease (induction and maintenance)
Van Assche[192] (IMID)	2008	80 (80)	IFX+AZA or MTX IFX	104	60 55	–	NS	Responders to IFX + AZA for at least 6 months (in remission at entry)
Feagan[41] (COMMIT)	2008	126 (126)	IFX 5 mg/kg IFX+MTX	50	56 [c] 57 [c]	–	NS	Patients with active disease (induction with steroids + IFX)
Colombel[1] (SONIC)	2008	508 (508)	IFX 5 mg/kg IFX+AZA AZA	26	44 [c] 57 [c] 30 [c]	–	0.02 [d] <0.001 [d]	Patients with active disease (induction and maintenance)

AZA = azathioprine; MTX = methotrexate,CTZ = certolizumab pegol, IFX = infliximab, ADA = adalimumab.

[a] Clinical remission rate was not the primary endpoint and was not reported in the article; information obtained from the authors is available in the Cochrane Database Systematic Review [*Behm 2009*].

[b] Primary endpoint was steroid withdrawal.

[c] Primary endpoint was steroid-free remission.

[d] *Versus* IFX+AZA.

$p<0.0001$) and clinical response (RR 2.19; 95% CI 1.27 to 3.75; $p=0.005$). Infliximab was also superior to placebo for corticosteroid-sparing effects (RR 3.13; 95% CI 1.25 to 7.81; $p=0.01$). There were no significant differences in remission rates between infliximab doses of 5 mg/kg or 10 mg/kg. Compared with placebo, certolizumab pegol 400 mg every 4 weeks was also found to be effective for maintenance of clinical remission (RR 1.68; 95% CI1.30 to 2.16; $p<0.0001$) and clinical response (RR 1.74; 95% CI 1.41 to 2.13; $p<0.00001$) to week 26 in patients who have responded to certolizumab therapy. The two studies evaluating adalimumab were evaluated separately due to heterogeneity among the participants. In CHARM,[27] adalimumab was found to be superior to placebo for maintenance of clinical remission to week 54 (RR 3.28; 95% CI 2.13 to 5.06). In CLASSIC 2,[184] adalimumab was also found to be superior to placebo for maintenance of clinical remission to week 54 (RR 1.82; 95% CI 1.06 to 3.13). There were no significant differences in remission rates between adalimumab 40 mg weekly or every other week. There was no evidence to support the use of CDP571 for the maintenance of remission in Crohn's disease. Although differences in trial durations limit direct comparisons of all data, the authors concluded that it appears likely that infliximab, adalimumab, and certolizumab pegol have similar clinical efficacy in patients with Crohn's disease. Adverse events were observed in approximately equal frequencies in the treatment and placebo groups, but they noted that serious adverse events, including tuberculosis and lymphoma, were reported in several trials.

The ACCENT 1 study has been re-analysed[185] to compare episodic and scheduled treatment strategies. This included all 573 patients (responders and non responders) and compared regularly scheduled maintenance (infliximab groups) and episodic maintenance (placebo group). Mean CDAIs were significantly better in the 10 mg/kg scheduled group from weeks 10 to 54, while response and remission rates in the combined 5 and 10 mg/kg scheduled-treatment were higher from weeks 10 to 30. A lower proportion of patients developed antibodies to infliximab in the scheduled-treatment groups. Perhaps most relevant was the observation that patients in scheduled strategy had fewer Crohn's disease-related hospital admissions and surgery compared to those in the episodic strategy.

The value of combining anti-TNFα with immunosuppressant agents such as azathioprine or methotrexate is still debated. Some studies have shown that the use of concomitant immunosuppressant therapy may reduce the risk of antibodies directed against infliximab and improve efficacy, but these data mostly come from studies using episodic infliximab therapy.[187,188] In the ACCENT I trial, reduced antibody formation was observed when an induction regimen is followed by maintenance treatment compared to a single dose followed by episodic treatment (8 vs. 30%; $p<0.001$),[77,115,186] but concomitant immunomodulatory therapy with infliximab was not associated with better clinical outcome when 3-dose induction was followed by scheduled maintenance therapy. These findings are consistent with analyses of the impact of baseline concomitant immunosuppressants performed on data from maintenance trials with other anti-TNFα (adalimumab, certolizumab).[27,28,182] In an open-label, randomized, controlled trial, Van Assche et al.[189] have shown that during maintenance therapy with infliximab, the continuation of immunosuppressive therapy for more than 6 months offers no clinical benefit over ongoing infliximab monotherapy, but is associated with higher infliximab trough levels. Feagan et al.[41] have reported the results of a randomized, placebo-controlled study to evaluate the efficacy of infliximab in combination with methotrexate. Patients with active Crohn's disease who had corticosteroid therapy initiated within 6 weeks were randomized to methotrexate or placebo for up to 50 weeks. Both groups received induction and maintenance infliximab therapy for up to 50 weeks. High rates of corticosteroid-free remission over one year were demonstrated with both regimens (56% and 57%) but triple induction therapy (prednisone+methotrexate+infliximab) followed by methotrexate+infliximab maintenance therapy was not more effective than dual induction therapy (prednisone+infliximab) followed by infliximab maintenance therapy. In contrast, the results of a randomized, double-blind study of 508 patients with active Crohn's disease who were naïve to immunomodulator and anti-TNF biologic therapies (SONIC) were recently reported.[1] Combination therapy with infliximab and azathioprine was superior to infliximab and azathioprine monotherapies during the first 6 months of the study; during the same period, safety results were similar among the three treatment groups. It is thus possible that there may be greater efficacy with concomitant immunomodulators in naïve patients but not in those who have already failed these drugs. [116] Available data also suggest an increased risk of hepatosplenic T-cell lymphoma when azathioprine in combination with infliximab therapy is administered.[190] However there is no evidence of a higher risk of opportunistic infections with the combination of azathioprine and infliximab as compared to azathioprine or infliximab alone.[1,59,60,191]

6.2.7.2. Summary. There is evidence that infliximab [EL1a], adalimumab [EL1a], and certolizumab pegol [EL1b] are effective for maintenance of remission in patients with luminal Crohn's disease who have a clinical response to induction therapy. Infliximab and adalimumab are currently approved for use in Crohn's disease in many countries, while certolizumab pegol is not approved in the European Union.

6.2.8. Other biologic therapies

Natalizumab, a humanized anti-α4 integrin monoclonal antibody, was investigated for maintenance of response and remission in Crohn's disease (ENACT-2 study): 339 patients with a response (ΔCDAI ≥ -70) or remission after induction with natalizumab (ENACT-1, a 905 patient induction study — see Active Disease Section 5.4.5) were allocated to receive infusions of placebo or 300 mg of natalizumab every 4 weeks for 12 months.[79] Maintenance natalizumab resulted in higher rates of sustained response (61% vs 28%, $p<0.001$) and remission (44% vs 26%, $p=0.003$) through week 36 than did switching to placebo. Despite this promising result for maintenance, treatment with natalizumab has not been approved in the European Union partly due to cases of progressive multifocal leucoencephalopathy occurred in several patients with multiple sclerosis and one patient with Crohn's disease.[192]

Other biologic therapies are under evaluation in Crohn's disease including anti-adhesion molecules (MLN-02, alicaforsen, CCX-282-B), anti-inflammatory cytokines (interleukin 10, interleukin 11, and interferon-beta), anti-IL12 p40 antibody (ustekinumab, ABT-874), anti-interferon-gamma

(fontolizumab), anti-IL-6 (tocilizumab), anti-CD28 (abatacept) anti-CD3 (visilizumab) or anti-CD4 (cM-T412) antibodies, G-CSF (filgastrim) or GM-CSF (sargramostrim) and growth hormone (somatropin). Promising results have been reported in IBD with several of these novel biologic therapies,[78,193] but none have yet been evaluated for maintenance of remission in Crohn's disease.

6.2.9. Diet therapy

6.2.9.1. Omega-3 fatty acids

6.2.9.1.1. Evidence. Preparations containing omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) may have anti-inflammatory properties by reducing the production of leucotriene B4. A clinical trial including 204 patients compared a preparation containing EPA 3.3 g/day and DHA 1.8 g/day (Maxepa®) to placebo for 12 months, without any significant benefit.[194] A second study included 78 patients treated with another preparation containing EPA and DHA (Purepa®). At one year the rate of patients in remission was 59% in the treated group and 26% on placebo ($p=0.03$).[195] Two Phase III studies (EPIC-1 and EPIC-2) with a similar enteric-release formulation of omega-3 fatty acids (Epanova®) were reported in 2008. EPIC-1 is a double-blind, placebo-controlled trial of 52 weeks duration including 383 patients with Crohn's disease who were in remission (CDAI<150) for at least three months at baseline, and had at least one exacerbation within the previous year.[196] Two time release 1 g gelatin capsules of n-3 twice daily (approximately 2.2 g/d of EPA and 0.8 g/d of DHA) versus identical placebo of four 1 g capsules containing medium-chain triglyceride oil were administered. EPIC-2 is a double-blind, placebo-controlled trial of 58 weeks duration including 379 patients with active disease who were treated with a standardized 16-week tapering course of either prednisone or budesonide.[196] If the CDAI score was <150 points 8 weeks after the initiation of corticosteroids, the patient was eligible for randomization to treatments similar to the EPIC-1 trial. In both EPIC-1 and EPIC-2 trials, no significant difference in the relapse rate was found between the patients treated with n-3 or placebo. Romano *et al.*[197] also reported a double-blind, placebo-controlled trial of one year duration in 38 children with Crohn's disease in remission at baseline (PCDAI<20 for at least two months). 5-ASA (50 mg/kg/day)+n-3 in gastro-resistant capsules (Triolipsofar®) containing 1.2 g/day of EPA and 0.6 g/day of DHA, versus identical placebo of 5-ASA (50 mg/kg/day)+olive oil were administered. A very high relapse rate was found in the placebo group ($n=19/20$, 95%) compared with $n=11/18$, 61% in the n-3 group ($p<0.001$). A Cochrane Database systemic review was published after the Consensus[198] including the six RCT and one additional study in patients with surgically-induced remission. There was a marginal significant benefit of n-3 therapy for maintaining remission (RR 0.77; 95% CI 0.61 to 0.98; $p=0.03$). However, the studies were heterogeneous ($p=0.03$; I2=58%) and a funnel plot suggested publication bias. No serious adverse events were recorded in any of the studies but in a pooled analyses there was a significantly higher rate of diarrhoea (RR 1.36 95% CI 1.01 to 1.84) and symptoms of the upper gastrointestinal tract (RR 1.98 95% CI 1.38 to 2.85) in the n-3 treatment group.

6.2.9.1.2. Summary. For maintenance of medically induced remission in Crohn's disease, the efficacy of omega-3 fatty acids remains controversial, due to inconsistent results seen in the literature [EL1b]. The existing data do not support use omega 3 fatty acids.

6.2.9.2. Nutritional supplementation

6.2.9.2.1. Evidence. Two studies aimed to evaluate the efficacy of enteral nutrition for the maintenance of remission in Crohn's disease in adult patients. Verma et al.[199] compared oral supplementation with elemental diet in addition to normal diet to an unrestricted diet in a series of 39 patients with Crohn's disease in clinical remission. On an intention-to-treat basis, 10/21 patients (48%) in the supplemented group remained in remission for 12 months, compared to 4/18 (22%) patients in the control group, $p<0.0003$. Four of the 21 patients (19%) were intolerant to enteral feeding. Takagi et al.[200] evaluated the effectiveness of home enteral nutrition as a maintenance therapy using a diet in which half of the daily calorie requirement is provided by an elemental diet and the remaining half by a free diet. Fifty-one patients in remission were randomly assigned to a half elemental diet group ($n=26$) or a free diet group ($n=25$). The relapse rate in the half elemental diet group was significantly lower [34.6% vs. 64.0%; multivariate hazard ratio 0.40 (95% CI: 0.16–0.98)] than that in the free diet group after a mean follow-up of 11.9 months. In the Cochrane Database Systematic Review by Akobeng et al.[201] statistical pooling of the results from these two trials was not possible because both the control interventions and the way in which outcomes were assessed differed greatly between the two studies. They did not confirm the superiority of supplementation with elemental diet in the Verma study (OR 0.97, 95% CI 0.24 to 3.92).

6.2.9.2.2. Summary. There is no enough evidence to support that enteral nutritional supplementation is effective for the maintenance of remission in Crohn's disease [EL1b].

6.2.10. Probiotics

6.2.10.1. Evidence. Clinical trials evaluating the efficacy of probiotics including *E. coli* Nissle 1917, *Saccharomyces boulardii* and *Lactobacillus* GG for maintenance of medically induced remission in luminal Crohn's disease are listed in Table 6.7.[202–206] In a Cochrane Database Systematic Review, Rolfe et al.[207] examined the role of probiotics in the maintenance of surgically-induced (2 trials) or medically induced (5 trials) remission in Crohn's disease. All of the studies included small numbers of patients and may have lacked statistical power to show differences should they exist. Compared to placebo, there was no statistically significant benefit of *E. coli* Nissle (RR 0.43, 95% CI 0.15 to 1.20) or *Lactobacillus GG* (RR 0.83, 95% CI 0.25 to 2.80) for reducing the risk of relapse there was no statistically significant benefit of probiotics for reducing the risk of relapse compared to maintenance therapy employing aminosalicylates or azathioprine (RR 0.67, 95% CI 0.13 to 3.30).

6.2.10.2. Summary. There is no enough evidence to suggest that probiotics are beneficial for the maintenance of remission in Crohn's disease [EL1b].

Table 6.7 Placebo-controlled trials of probiotics for maintenance of medically induced remission in Crohn's disease.

Author [ref.]	Year	Nb of randomized patients (initial population)	Drug (mg/Kg/day)	Duration (months)	Relapse rate (%)			Randomized patients
					Probiotics	Placebo	*p*	
Malchow[202]	1997	20 (28)	*E. coli* 1917 (200 mg/d)	12	30	70	NS	Patients with active colonic disease on a steroid-tapering regimen. ncluded when remission (CDAI<150) was achieved
Guslandi[203]	2000	32	*S. boulardi* 1 g/d+MSZ 2 g/d	6	6	–	0.08	Patients in remission for at least 3 months
			MSZ 3 g/d		37	–		
Zocco[204]	2003	35	*Lactobacilli GG* 18 billion/d	12	17	–	NS	Patients in remission
			MSZ 2.4 g/d		25			
			Lactobacilli GG+MSZ		18			
Schultz[205]	2004	9 (11)	*Lactobacilli GG* 20 billion/d	6	50	60	NS	Patients with active disease treated for 2-week with antibiotics and a 3-month steroid-tapering regimen
Bousvaros[206]	2005	75	*Lactobacilli GG* 20 billion/d	10	31	17	NS	Children in remission (PCDAI<10) on other maintenance therapies at entry (5-ASA, thiopurines, low-dose of steroids)

MSZ = mesalazine.

6.2.11. Cytapheresis and autologous stem cell transplantation

The effectiveness of lymphapheresis was studied in 28 patients in clinical remission induced by steroids. After 18 months, the rate of relapse was 83% in the lymphapheresis group and 62% in the control group (ns).[208] Adacolumn® and Cellsorba® leukocyte filters have also been proposed for leucocyte apheresis, but to date, only a few case series and open studies have evaluated its efficacy in active Crohn's disease, with variable results.[209] No study is available for maintenance of medically induced remission.

Oyama et al.[210] conducted a phase 1 study in 12 patients with active Crohn's disease despite conventional therapies including infliximab. Peripheral blood stem cells were mobilized with cyclophosphamide and granulocyte colony-stimulating factor and CD34+ enriched. Eleven of 12 patients entered a sustained remission. After a median follow-up of 18 months, only one patient has developed a recurrence. The procedure was well-tolerated. Other authors have shown similar results in a limited series.[211] Randomized controlled trials are ongoing.

6.2.12. General conclusion

Medications whose efficacy for maintaining medically induced remission in Crohn's disease is well established [EL1a] include azathioprine, infliximab and adalimumab. There is also a reasonable level of evidence [EL1b] for methotrexate, certolizumab and natalizumab [EL1b]. The efficacy of mesalazine [EL1b] and omega-3 fatty acids [EL1b] remains controversial, due to inconsistent results. There is not enough evidence to support the use of enteral nutritional supplementation, *S. boulardii*, *E. coli* Nissle 1917, cytapheresis and autologous stem cell transplantation. The available evidence shows that ciclosporin, anti-mycobacterial agents, CDP571, and *Lactobacillus* GG are ineffective.

7.0. Surgery for Crohn's disease

7.1. Introduction

Since it is impractical to cover all surgical aspects of the management of Crohn's disease, this Consensus will addresses areas of interest and controversy. The surgical management of Crohn's disease has changed considerably during the last decade as a result of developments in medical therapy. Although most patients will still, eventually, have surgery, the care of Crohn's disease is now primarily in the hands of medical gastroenterologists. This mandates the gastroenterologist to understand the value of surgery in terms of symptom relief, and balance this against the risks of the procedure, so that the best therapy can be offered at the optimal time. Traditionally surgery and medicine have been regarded as complementary treatments for Crohn's disease. This may change, because drugs are evolving rapidly and symptomatic relief may be achieved by secondary or tertiary medical therapy. Surgery may then be consigned to the treatment of last resort. It must be recognised that this carries implicit risk, because those patients who come to surgery will have more

complicated disease and are likely to be at higher risk of septic complications.

The evidence on which surgical therapy is based includes very few prospective randomized studies. However, there is good evidence that extensive resection is no longer necessary and potentially harmful.[212] Consequently, the trend is to leave diseased bowel behind, just dealing with the part of the bowel responsible for the symptoms that invoked surgical treatment. The risk of short bowel syndrome due to extensive bowel resection is probably much lower with this strategy. When patients with Crohn's disease do end up with intestinal failure, it is usually a consequence of multiple operations within a short time span, after the primary operation has failed due to septic or other complications, rather than operations over several years for recurrent disease.

7.2. Small intestinal or ileocolonic disease

7.2.1. Localised ileal or ileocaecal disease

ECCO Statement 7A
Localised ileocaecal Crohn's disease with obstructive symptoms, but no significant evidence of active inflammation, should be treated by surgery [EL2b, RG C].

Patients with inflammatory Crohn's disease confined to the ileo-caecum with a maximum of 40 cm affected bowel and appreciable symptoms (CDAI>220) but no imminent obstruction respond well to steroid treatment. However, this patient group will almost always require surgery during the course of their disease. Following resection, long-term studies have demonstrated that there is a 50% chance that the patient will never require a further operation (i.e. have symptoms of the same severity again).[213–216] In contrast there are no long-term follow-up studies (i.e. >15 years) of the outcome of medical treatment. In addition, it is not known whether there are long-term differences in the quality of life of patients treated by medical as opposed to surgical therapy. Primary surgery should be considered as the first choice for patients with refractory obstructive symptoms after initial medical treatment (steroids) in ileocaecal Crohn's disease. Likewise, patients presenting with obstruction without inflammatory activity, for example assessed by C-reactive protein (CRP) levels,[217–219] can also be treated with primary surgery. If, however, the patient has had previous ileocaecal resection and anastomotic stenosis has occurred, endoscopic dilatation could be tried before moving to an intestinal resection.[4,220]

7.2.2. Concomitant abscess

ECCO Statement 7B
Active small bowel Crohn's disease with a concomitant abdominal abscess should preferably be managed with antibiotics, percutaneous or surgical drainage followed by delayed resection if necessary [EL3, RG C].

When active small bowel Crohn's disease is associated with a concomitant abdominal abscess, the consensus favours percutaneous drainage and delayed resection if there are obstructive symptoms. Drainage followed by medical treatment should be considered if there are no obstructive symptoms, depending on the clinical situation. Some abscesses do not lend themselves to percutaneous drainage. There are no randomized studies in the literature to clarify whether percutaneous or surgical drainage should always be followed by a delayed resection, and although most case series favour a delayed elective resection, opinions vary.[221–223]

7.2.3. Stricturoplasty

ECCO Statement 7C
Stricturoplasty is a safe alternative to resection in jejuno-ileal Crohn's disease, including ileocolonic recurrence, with similar short-term and long-term results. Conventional stricturoplasty is advised when the length of the stricture is <10 cm. However, in extensive disease with long strictured bowel segments where resection would compromise the effective small bowel length, non-conventional stricturoplasties may be attempted [EL2a, RG C].

Most authors limit conventional stricturoplasties to strictures <10 cm in length. The majority opinion is that stricturoplasty is inadvisable for longer (>10 cm) strictures. However, there are now series reported with non-conventional stricturoplasties for longer bowel segments, reporting good results.[224–229] A phlegmon in the bowel wall, carcinoma, or active bleeding with mucosal disease are contraindications to stricturoplasty. Where there are multiple strictures in a short segment and where bowel length is sufficient to avoid short bowel syndrome, resection may be preferable.

Recent systematic reviews[230,231] and patient series[232] comparing stricturoplasty and resection have confirmed the safety and bowel-sparing potential of strictureplasty for small bowel Crohn's disease. The question whether resection may induce a longer recurrence-free survival has not been resolved.[231,233] There are several case reports of adenocarcinoma at strictureplasty sites,[234] rendering the need for a certain caution over the long-term consequences of the procedure.

7.2.4. Anastomotic technique

ECCO Statement 7D
There is evidence that a wide lumen stapled side-to-side (functional end-to-end) anastomosis is the preferred technique [EL2a, RG B].

The observation that recurrent Crohn's disease almost invariably appears just proximal to the anastomosis has led to the assumption that the width of the anastomosis matters. Several studies have tried to address this.[235–240] A recent meta-analysis[241] of 8 comparative studies (2 RCTs) published

between 1992 and 2005 comparing end-to-end anastomosis and stapled side-to-side anastomotic configurations including 712 anastomoses in 661 patients showed that end-to-end anastomosis after ileocolonic resection for Crohn's disease was associated with increased anastomotic leak rates and overall post-operative complications. There was no significant difference with regard to peri-anastomotic recurrence rates. Thus, there is evidence to support the choice of stapled side-to-side anastomosis in this patient group. On the other hand, a recent prospective cohort study showed no difference in safety and recurrence rate between hand-sewn side-to-side and stapled side-to-side anastomosis,[236] which may imply that a wide anastomotic luminal diameter is the discriminating factor, rather than the suturing technique used.

7.2.5. 'Coincidental' ileitis

ECCO Statement 7E
Terminal ileitis resembling Crohn's disease found at a laparotomy for suspected appendicitis should not routinely be resected [EL5, RG D].

The finding of terminal ileitis or caecitis at laparoscopy or laparotomy for a clinical suspicion of appendicitis is non-specific, and it is virtually impossible to differentiate between Crohn's disease and infectious (e.g. *Yersinia* species) enteritis. Even if it were to be Crohn's ileitis, resection might not be the most appropriate strategy if the dominant symptoms relate to inflammation. Only when the patient's history indicates obstructive symptoms for more than a few days, or the proximal intestine is dilated and the inflamed bowel wall looks typical of Crohn's disease with mesenteric fat wrapping, is an experienced surgeon justified in performing a primary resection.[242]

7.2.6. Laparoscopic resection

ECCO Statement 7F
A laparoscopic approach is to be preferred for ileocolonic resections in Crohn's disease [EL 2A, RG B] where appropriate expertise is available. In more complex cases or recurrent resection, there is insufficient evidence to recommended laparoscopic surgery as the technique of first choice [EL3, RG C].

Several studies during the last few years have shown that laparoscopic resection gives substantial benefits in addition to a shorter scar. The literature previously contained mostly retrospective and non-randomized studies.[243–245] However, two recent meta-analyses of 14 and 15 studies, respectively (with 10 of the studies included in both) showed benefits in the post-operative period for the laparoscopic group. Advantages included earlier recovery of normal intestinal function, shorter hospital stay and lower post-operative morbidity.[246,247] This was also confirmed in a US nationwide registry study of 49,609 resections for Crohn's disease.[248] The 2826 cases (6%) done laparoscopically were associated with shorter length of stay, lower charges, a lower complication rate (8% vs. 16%), and reduced mortality (0.2% vs. 0.9%, $p<0.01$). There has been debate about the heterogeneity inherent in a meta-analysis, which may also apply to the registry study. However, the most important findings of reduced morbidity are similar in recent randomized trials,[249,250] which also report better results with fewer complications and shorter hospital stay compared to conventional surgery for selected patients undergoing ileocolic resection for Crohn's disease. The 10-year follow-up of a randomized trial comparing open and laparoscopic resection for ileocolic Crohn's showed equal rates of surgical recurrence.[251] Moreover, better cosmesis scores and body image in the laparoscopy groups have also been reported[252]; important parameters to consider in this young patient group. Thus, although laparoscopic surgery for Crohn's disease is technically demanding, there is emerging evidence for significant advantages with the technique for primary ileocolonic resections.

Although extrapolated from surgery for other diagnoses, there is also a potential benefit from laparoscopy in reducing ventral hernias and adhesion formation.[253]

This may make it possible to perform repeat IBD surgery via the laparoscopic approach. Evidence for feasibility and safety in complex Crohn's is scarce[254] with recurrent disease and intra-abdominal abscess or fistulae being important risk factors for conversion to open laparotomy.[255] A high conversion rate is pertinent when dealing with complex IBD surgery to ensure patient safety. Laparoscopic surgery in complex cases should currently only be done at highly specialized centres and preferentially within clinical studies.

7.3. Crohn's disease of the colon

7.3.1. Localised colonic disease

ECCO Statement 7G
If surgery is necessary for localised colonic disease (less than a third of the colon involved) then resection only of the affected part is preferable [EL3, RG C].

Limited colonic Crohn's disease treated by segmental resection results in a higher rate of recurrence than a proctocolectomy.[237,256–260] However, most agree that the avoidance of a permanent stoma usually outweighs the increased risk of recurrence.

7.3.2. Multi-segment colonic disease

ECCO Statement 7H
Two segmental resections can be considered for a patient with an established indication for surgery when macroscopic disease affects both ends of the colon [EL3, RG C].

The consensus is less clear when it comes to a patient with macroscopic disease in two widely separated segments of the colon. Half of the experts felt that segmental resection of

the macroscopic disease and two anastomoses are acceptable. Others believed that a subtotal colectomy with an ileorectal anastomosis should be performed when macroscopic disease affects the ascending and the whole of the sigmoid colon, assuming that surgery is indicated. There is some support for separate segmental resection in the literature.[260] Decisions should take individual preferences of the patient and surgeon into account.

7.3.3. Dilatation of strictures

ECCO Statement 7I
Endoscopic dilatation of stenosis in Crohn's disease is a preferred technique for the management of accessible short strictures. It should only be attempted in institutions with surgical back-up [EL2a, RG B].

Endoscopic dilatation is an accepted technique for the management of mild to moderate stenosing disease. Outcomes suggest a short to midterm benefit.[261,262] Most experts consider that dilatation of a stenosis in Crohn's disease should only be attempted in institutions with a 24-h surgical service. The literature does not provide any guidance on this, although perforation and other complications requiring surgical intervention can occur.[263] A recent review of 13 studies enrolling 347 Crohn's disease patients treated with endoscopic dilatation for postsurgical strictures reported an 80% technical success rate. A stricture length $<$ or $=$ 4 cm was associated with a surgery-free outcome although major complications including perforation occurred in 2%.[220] It was concluded that endoscopic dilatation is effective and safe, especially for recurrence after ileocolonic resections, delaying surgery by a mean of 3 years.

7.3.4. Colonic stricturoplasty

ECCO Statement 7J
Stricturoplasty in the colon is not recommended. [EL4, RG D]

Most experts agree that stricturoplasty is not an option for strictures in the colon, although there is insufficient evidence in the literature. A particular concern is the increased chance of cancer in a colonic stricture compared to the small bowel. One retrospective report indicates that stricturoplasty for large bowel stenoses in Crohn's disease is feasible.[264]

7.3.5. Ileopouch-anal anastomosis

ECCO Statement 7K
All the available evidence suggests that in patients with an unsuspected diagnosis of Crohn's disease after IPAA there are higher complication and failure rates. At present an IPAA is not recommended in a patient with Crohn's colitis. [EL2a, RG B].

Most IPAA series include some patients with Crohn's disease. Retrospective analyses show that these patients suffer a higher complication rate, with pouch failure reported in up to 50%.[265–269] However, one group reports a very small increase in morbidity compared to patients with ulcerative colitis.[270,271] Some suggest this may reflect differences in pathological diagnosis. A recent meta-analysis[272] of outcomes of IPAA in Crohn's disease did, however, show more anastomotic strictures and incontinence in patients with Crohn's disease. Moreover, pouch failure was 6-fold more frequent than with ulcerative colitis and indeterminate colitis. This has been confirmed in other large single-centre series.[273,274] Half the experts are prepared to recommend an IPAA for a patient with long-standing Crohn's colitis, provided there is no sign of small bowel or perianal disease, and that the patient is willing to except an increased risk of complications and pouch failure. Many would hesitate strongly to recommend this.

7.4. Surgery and medication

7.4.1. Surgery after anti-TNF therapy

ECCO Statement 7L
Whether there is a higher rate of post-operative complications from abdominal surgery during or after anti-TNF therapy remains controversial [EL3, RG D]. The safe interval remains to be determined.

TNFα is a key player in the immune response. Therefore, inhibition by anti-TNF therapy could potentially lead to serious post-operative complications. Although the initial published literature did not support this theory,[275,276] recent studies report conflicting data. Appau et al.[277] compared 30-day post-operative outcomes for Crohn's patients treated with infliximab within 3 months prior to ileocolonic resection. The infliximab and non-infliximab groups had similar disease characteristics. Multivariate analysis showed infliximab use to be associated with 30-day post-operative readmission ($p=0.045$), sepsis ($p=0.027$), and intra-abdominal abscess ($p=0.005$). Although this study contradicts previous studies, its strength is that it concentrates on ileocolonic anastomoses after preoperative anti-TNF treatment. In another recent series of a mixed IBD population,[278] anti-TNF treatment was not associated with an increased rate of post-operative complications. There is no consensus among experts as to the optimum time between treatment with an anti- TNF agent and abdominal surgery, with equal proportions suggesting one month, a longer period, or that it does not matter. There is almost no evidence from the literature. The pharmacokinetics of monoclonal antibodies is such that therapeutic concentrations generally persist after an infusion for at least 8 weeks.

7.4.2. Patients on steroids

ECCO Statement 7M
Prednisolone 20 mg daily or equivalent for more for more than six weeks is a risk factor for surgical complications [EL2b, RG B]. Therefore, corticosteroids should be weaned if possible [EL5, RG D].

A third of experts agree that treatment with steroids is a risk factor for post-operative complications. Uncontrolled or retrospective series indicate that patients taking $\geq$20 mg prednisolone for $>$6 weeks do have an increased risk for surgical complications.[58,277]

7.4.3. Patients on thiopurines

ECCO Statement 7N
Azathioprine can safely be continued in the peri-operative period and beyond [EL2b, RG B].

Most publications agree that azathioprine does not increase the risk of surgical complications,[58,279,280] although some question this.[281]

7.5. Surgical decision making

7.5.1. Surgery and medicine are complementary

ECCO Statement 7O
In complicated Crohn's disease, surgery at an early stage is a valid alternative to medical therapy [EL5 RG D].

It is important that patients with abscesses because of internal fistulas (enteric-bladder-vaginal) and/or stenotic bowel segments are considered for surgery at a relatively early stage of the disease rather than after prolonged immunosuppressive treatment that may increase the risk of sepsis and lead to compromised healing capacity. In these complex cases early surgery may in reality be the preferred top-down approach.[282]

Morbidity rates of long-term steroid use are well established. Biologics, particularly in combination with immune suppression, may also have long-term effects that currently are unknown. With this in mind, surgery must be viewed as a therapeutic alternative to immunosuppressive medication, rather than a last resort. The ongoing trial comparing infliximab treatment with surgery in recurrent distal ileitis in Crohn's disease[283] is a welcome and important effort in an area that is currently lacking evidence

ECCO Statement 7P
Multidisciplinary clinical conferences to discuss the treatment strategy of individual cases are recommended especially for the management of patients with complicated CD [EL5 RG D].

The increasing complexity and number of choices both in medical treatment and surgical options for patients with Crohn's disease makes it even more important to discuss each case in multidisciplinary clinical conferences. Correct diagnosis and assessment with optimised medical treatment are prerequisites for optimal surgical timing and good surgical outcomes. Therefore close interaction between the gastroenterologist, the colorectal surgeon and other disciplines are needed for optimal patient outcome over a life-long perspective.

7.5.2. Fitness for surgery

An essential part of surgical management involves the selection of patients for surgery. Fitness for surgery includes nutritional, medical, social and psychological factors. Smoking is a major risk factor for post-operative recurrence (OR 2.5) and all patients with Crohn's disease should be strongly recommended to stop smoking before undergoing surgery.[284] Although there is no body of evidence, nutritionally compromised patients with major weight loss ($>$10% in 3 months) are likely to benefit from a period of preoperative nutritional support, often requiring parenteral nutrition. Patients with a low serum albumin usually have uncontrolled sepsis and may or may not be nutritionally compromised. Such patients are likely to benefit from drainage of sepsis together with nutritional support.

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