ECCO Guidelines on Therapeutics in Crohn's Disease

medical treatment

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ECCO Guidelines on Therapeutics in Crohn's Disease: medical treatment

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Introduction

Crohn's disease [CD] is a chronic inflammatory bowel disease [IBD] that can result in progressive bowel damage and disability[1]. CD can affect individuals of any age, from children to the elderly,[2,3] and may cause significant morbidity and impact on quality of life. Up to one-third of patients present with complicated behaviour [strictures, fistula, or abscesses] at diagnosis[4]. Most patients over time will develop a complication, with roughly 50% of patients requiring surgery within 10 years of diagnosis[5-7]. As the precise aetiology of CD remains unknown, a curative therapy is not yet available[8]. Several agents are available for the medical treatment of CD. Medical agents include mesalazine [5-ASA], locally active steroids [such as budesonide], systemic steroids, thiopurines such as azathioprine [AZA] and mercaptopurine [MP], methotrexate [MTX], and biological therapies [such as anti-TNF, anti-integrins, and anti-IL12/23].

The European Crohn's and Colitis Organisation [ECCO] produces and regularly updates several guidelines aimed at providing evidence-based guidance on critical aspects of IBD care to all healthcare professionals who manage patients with IBD. To provide high-quality evidence-based recommendations on medical and surgical treatment in CD, ECCO decided to develop these guidelines by adopting the GRADE [Grading of Recommendations Assessment, Development, and Evaluation] approach[9]. GRADE is a systematic process for developing guidelines that addresses how to frame the healthcare questions, summarize the evidence, formulate the recommendations, and grade their strength and the quality of the associated evidence. GRADE increases transparency at all levels of this process and makes explicit the three considerations that lead to a particular recommendation: the quality of the evidence, the balance of benefits and harms, and the patients' values and preferences. Therefore, ECCO reviewed the available high-quality evidence on the medical management of CD and developed evidence-based recommendations on the medical treatment of adult patients with CD. These guidelines do not cover specific situations, such as post-operative management of adult patients with CD, which was already covered in the last ECCO Guidelines on Crohn's disease[10].

Methods

Based on the GRADE workflow, the Guidelines Committee of ECCO [GuiCom] selected a panel of 48 experts supported by a team of methodologists and librarians. Selection was based on IBD expertise, scientific background, and knowledge of the GRADE methodology. All panellists received adequate training in GRADE before starting the process. Additionally, four patients with CD representing the European Federation of Crohn's and Colitis Associations [EFCCA] were invited to participate in all face-to-face meetings and to provide their experiences and state their preferences.

Three domains for medical treatment of CD were identified:

1) induction therapy

2) maintenance therapy

3) therapy of fistulizing perianal disease.

All panellists were assigned to one of three working groups coordinated by one to two working group leaders under the supervision of two Guideline coordinators. The panellists first formulated a series of specific questions using the PICO format [Population, Intervention, Comparator, Outcomes] that were deemed to be clinically important for the medical treatment of CD. The outcomes of all PICO questions were subsequently graded as "not important", "important", or "critical" during a face-to-face kick-off meeting in Vienna, using a Delphi consensus process.

A team of professional librarians performed a comprehensive literature search on EMBASE, PubMed/Medline, and Cochrane Central databases using specific search strings for each PICO question [Supplementary Files 1, 2, and 3].

Two independent working group members [one assigned to the PICO and another one from the same group as a second reviewer] assessed the relevance of each abstract to PICO and included or excluded all the relevant papers for the final data extraction and analysis. Subsequently, the working group members assigned to each PICO question systematically reviewed and summarized the evidence on every outcome to compile a Summary of Findings [SoF] table for each question. The GRADE method follows a hierarchical approach to synthesise evidence; recent high-quality systematic reviews and meta-analyses of clinical trials were preferentially used to create the recommendations. When these were not available, individual randomized clinical trials [RCTs] followed by observational studies were reviewed; results of individual studies were pooled using random-effects meta-analysis as appropriate and when needed. To define disease activity and severity [mild-to-moderate and moderate-to-severe], we accepted the definitions used by the investigators of the studies selected as an evidence basis for our work.

The quality of evidence was classified into the following four categories in accordance with the GRADE approach: "**high**" [meaning that further research is unlikely to change our confidence in the effect estimates], "**moderate**" [further research may change our confidence in the effect estimates], "**low**" [further research likely to change our confidence in the effect estimates], and "**very low**" [meaning that any estimate of effect is very uncertain][9]. For each PICO question, the quality of evidence was equal to the lowest quality of evidence among those outcomes graded as "critical". The strength of each recommendation was graded as either "**strong**" [meaning the desirable effects of an intervention clearly outweigh the undesirable effects, or vice versa] or as "**weak**" [meaning the balance is less certain], considering also the quality of evidence, values or preferences, and resource use. Whenever the chosen outcomes were not reported in the clinical trials, this was indicated in the corresponding SOF table. To support the recommendations, we either extracted summary effect estimates from the preselected systematic reviews or our group of methodologists directly performed the comparisons. All recommendations were subject to online voting by the panel members, the ECCO National Representatives [two for each country affiliated with ECCO], and 13 additional reviewers from a list of ECCO members who applied to the open call but were not selected to be part of the Working Groups [see acknowledgments section]. The final version of all statements/recommendations was discussed among panel members during a final consensus meeting in Vienna and put to a vote; final recommendations were approved if at least 80% of the panellists agreed with the statement and its associated strength grading. The list of statements, the supporting text and material, and the draft of the manuscript were critically reviewed by two external Guideline Committee members and by the ECCO Governing Board members, who also approved the final version of these Guidelines.

The literature search strategies, the relevant definitions of patient populations and outcomes, a detailed description of the process, and the SoF tables summarizing the evidence can be found in the Supplementary Material.

General approach to the medical treatment of Crohn's Disease

As CD is a lifelong disease, therapy aims to induce remission in the short term and maintain remission in the long term. The recognition that chronic and untreated inflammation [even if asymptomatic] ultimately results in poor outcomes[11-14] has led to a recent paradigm shift in medical treatment and disease monitoring; it is nowadays recognized that early intervention and intensive monitoring may prevent complications[15,16]. Stratifying patients according to their prognostic risk factors and individualizing therapy are crucial steps to optimize patient management, although high-quality evidence is not currently available to support this approach. Many factors affect the choice of medical therapy. These include disease location, disease activity and severity, prior response to therapy, and presence of complications [i.e. perianal or fistulizing disease]. In addition, the individual risk factors for progression and complications, the individual patient's characteristics, and the costs and benefit/risk ratio of each drug should be considered. As there is often a disconnect

between clinical symptoms and underlying inflammation, it is of crucial importance to monitor disease and therapy at regular intervals based on objective and measurable markers [endoscopy, C-reactive protein (CRP), calprotectin, imaging][17]. This approach will provide the clinician with the possibility to adjust therapy if needed, thereby maximizing the probability of achieving tight control of the disease and inflammation, which is believed to be essential to prevent disease progression[16-18]. In addition to drug therapy, the management of CD should also involve a series of general healthcare maintenance measures. Patients should be encouraged to stop smoking, nutritional deficiencies should be corrected, therapy-related side effects [i.e. cancer and infections] should be monitored, and appropriate guidance or surveillance for vaccinations, osteoporosis, sun protection should be implemented, as detailed in prior ECCO guidelines, topical reviews, or both[17,19-23].

SECTION 1. INDUCTION OF REMISSION

Mild-to-moderate disease

5-ASA Compounds

Recommendation 1.1. ECCO CD Treatment GL [2019]

We suggest against the use of 5-ASA for induction of remission of Crohn's disease (weak recommendation, moderate-quality evidence).

We performed a meta-analysis of seven eligible RCTs that compared the use of oral 5-ASA [five trials][24-27,28] or sulphasalazine [two trials][29,30] with placebo in patients with active CD [Supplementary Material, SoF Table 1]. The dosage of 5-ASA administered ranged from 1 g to 3.2 g/day; patients with mild-to-moderate disease with ileal, ileo-colonic, or colonic disease were included. Overall, there was no significant effect for induction of **clinical remission** [Relative Risk (RR): 1.28; 95% Confidence Interval (CI): 0.97–1.69] [Supplementary Figure 1]. A recent Cochrane review also found no significant overall effect[31]. Both 5-ASA and sulphasalazine appeared to be well tolerated in our meta-analysis, as there was no significant increase in withdrawals due to **adverse effects** [AEs] when compared to placebo [RR: 1.13; 95% CI: 0.73–1.84] [Supplementary Figure 2].

Among the five trials of 5-ASA alone there was also no benefit over placebo for inducing **clinical remission** [RR: 1.27; 95% CI: 0.79–2.03] [Supplementary Figure 3]. No significant increase in withdrawal due to **AEs** was observed in trials that compared 5-ASA alone versus placebo [RR: 1.0; 95% CI:0.58–1.71] [Supplementary Figure 4]. One published network meta-analysis noted a small statistically significant effect on **clinical remission** among the study arms that evaluated 5-ASA daily doses of > 2.4g/day[32]. However, another network meta-analysis was unable to confirm any such dose effect[33]. A pooled analysis of three double-blind placebo-controlled trials of a slow-release preparation of 5-ASA reported a significantly greater **reduction in the Crohn's Disease Activity Index** [CDAI] with 5-ASA versus placebo[34]. However, the effect size [an 18-point greater reduction in CDAI score comparing 5-ASA and placebo] was not clinically significant.

Two trials compared sulphasalazine with placebo for **induction of clinical remission**. A pooled analysis showed a small effect of borderline statistical significance [RR: 1.38; 95% CI: 1.00–1.89] [Supplementary Figure 5]. This was not accompanied by any significant increase in withdrawals for **AEs** [RR: 1.88; 95% CI: 0.65–5.47] [Supplementary Figure 6]. Subgroup analyses in both trials suggested that the efficacy of sulphasalazine was limited to patients with colonic CD[29,30].

The use of topical 5-ASA [enema or suppository] for the treatment of CD has not been studied in RCTs.

Budesonide

Recommendation 1.2. ECCO CD Treatment GL [2019]

We recommend using budesonide for the induction of clinical remission in patients with active mild-to-moderate Crohn's disease limited to the ileum and/or ascending colon (strong recommendation, moderate-quality evidence).

A Cochrane systematic review and meta-analysis[35] included three RCTs[36-38] that compared budesonide at a dose of 9 mg/day to placebo [Supplementary Material, SoF Table 2]. Two of these trials[37,38] evaluated **clinical response** [defined as decrease in CDAI score ≥ 100 or total CDAI score ≤ 150] at 8 weeks. **Clinical remission** [CDAI score ≤ 150] at 8 weeks was reported in all three RCTs. Budesonide was superior to placebo for inducing **clinical response** [RR: 1.46; 95% CI: 1.03–2.07] and **clinical remission** [RR: 1.93; 95% CI: 1.37–2.73] in patients with mildly active CD in the small and/or large intestine limited to the ascending colon. As compared with conventional steroids [e.g. prednisolone], which are usually associated with many systemic side effects, budesonide presented high topical anti-inflammatory activity and low systemic absorption and bioavailability and therefore had a better safety profile. Budesonide was shown to be safe [**AEs**; RR: 0.98; 95% CI: 0.77–1.25] in the reviewed meta-analysis[35].

A Cochrane systematic review and meta-analysis from 2015 reviewed two RCTs[39,40] that compared budesonide at a dose of 9 mg/day to mesalazine up to 4.5 g/day. More recently, a Japanese trial[41] also evaluated budesonide versus mesalazine in patients with active CD [Supplementary Material, SoF Table 3]. All trials evaluated **clinical response** [decrease in CDAI ≥ 100 or total CDAI ≤ 150] and **clinical remission** [CDAI ≤ 150] at 8 weeks. Budesonide was not superior to mesalazine for inducing **clinical remission** [RR: 1.30; 95% CI: 0.98–1.72] in patients with mildly active CD in the small and/or large intestine [Supplementary Figure 7]. Nevertheless, **clinical response** was more frequently seen in patients receiving budesonide [RR: 1.22; 95% CI: 1.03–1.45] than in patients receiving mesalazine [Supplementary Figure 8]. The **safety** profile of both compounds was comparable, with similar **AE** [RR: 0.91; 95% CI: 0.79–1.05] and **serious AE** [RR: 0.94; 95% CI: 0.24-3.75] rates in both intervention groups [Supplementary Figures 9 and 10].

Antibiotics

Numerous studies have studied the efficacy of antibiotic treatment on luminal CD. Metronidazole, ciprofloxacin, and anti-mycobacterial regimens have been extensively studied. Overall, none has demonstrated efficacy to consistently induce **clinical remission** or mucosal healing compared to placebo[42-44]. In addition, side effects limit the use of these therapies; recently, the European Medicines Agency has imposed restrictions on the use of ciprofloxacin due to disabling or potentially permanent events [EMA/668915/2018]. Therefore, a recommendation was not made specifically on antibiotics to treat luminal CD, although they remain indicated for the treatment of septic complications.

Moderate-to-severe disease

Systemic corticosteroids

Recommendation 1.3. ECCO CD Treatment GL [2019]

In patients with active, moderate to severe Crohn's disease, we suggest the use of systemic corticosteroids for the induction of clinical response and remission (weak recommendation, moderate-quality evidence).

Two RCTs reported on the efficacy of systemic corticosteroids [oral prednisolone or oral methylprednisolone] compared with placebo for the treatment of moderately to severely active CD[29,30][Supplementary Material, SoF Table 4]. Oral methylprednisolone was administered at a dose of 48 mg/day and reduced on a weekly basis to 32 mg, 24 mg, 20 mg, 16 mg, and 12 mg[29]. Doses of oral prednisolone ranged from 0.50 to 0.75 mg/kg with a maximum daily dose of 60 mg[30]. Prednisolone is usually tapered at 5 mg/week over an 8 to 12-week period. Data from these studies have been synthesized in a Cochrane systematic review[45].

One trial involving 105 patients reported on induction of **clinical response**[29]. **Clinical response** was more common in patients receiving methylprednisolone as compared with placebo [93.6% vs. 53.4%; RR: 1.75; 95% CI: 1.36–2.25]. Corticosteroids were reported to be twice as effective in inducing **clinical remission** than placebo in the two studies involving 267 patients [RR: 1.99; 95% CI: 1.51–2.64][45]. Data on the proportion of patients experiencing **AEs** from the use of systemic corticosteroids was available from one trial involving 162 patients treated with oral prednisolone[30,46]. The frequency of **AEs** was five-fold higher in patients receiving corticosteroids compared with placebo [31.8% vs. 6.5%; RR: 4.89; 95% CI: 1.98–12.07]. Steroid-related **AEs** included Cushing syndrome, acne, infection [increased risk of abdominal and pelvic abscesses in patients with CD], ecchymoses, hypertension, diabetes mellitus, osteoporosis, cataracts, glaucoma, and growth failure in children. Imprecision was serious for the outcomes considered due to sparse data, which yielded a moderate quality of evidence overall.

Immunosuppressants

Thiopurines

Recommendation 1.4. ECCO CD Treatment GL [2019]

We suggest against the use of thiopurines as monotherapy for the induction of remission of moderate-to-severe luminal Crohn's disease (weak recommendation, very low-quality evidence).

Several studies have reported on the use of thiopurines compared with placebo for induction of remission and response in CD[30,47-53] [Supplementary Material, SoF Table 5]. Five trials evaluated the use of thiopurines for **induction of clinical remission** [12–17 weeks] in comparison with placebo[30,47,48,51] [using CDAI or Harvey-Bradshaw index]. Overall, 380 patients were analysed. The active comparator was AZA in four of these trials,[30,47,51] while the active drug was MP in the remaining trial[54]. The trials were heterogeneous in terms of study design, follow-up time, definition of active disease, and definition of remission. Except for Summers *et al.*[30], most of the trials allowed for the use of concomitant steroids. The pooled analysis was performed in an intention-to-treat basis and revealed no differences **for induction of remission** between thiopurines and placebo; 48% [95/197] in the active intervention compared with 37% [68/183] in the placebo group achieved remission [RR: 1.23; 95% CI: 0.97–1.55].

Three trials reported on **clinical response**, albeit not with standardized measures of disease activity[49,52,53]. In these trials, different types of physician global assessment of disease improvement [**clinical response**] were used[49,52,53]. Overall, 42.8% of the patients receiving thiopurines, as compared with 26.9% of those receiving placebo, showed clinical improvement. The RR of obtaining **clinical response** was 1.87 [95% CI: 0.44–7.96]. Heterogeneity was serious [I^2 = 69%] and imprecision very serious due to sparse data and wide confidence intervals, thus the quality of evidence was very low for this outcome [Supplementary Figure 11].

Only one trial reported on **AEs** during induction[51]. The pooled RR of any **AEs** was not significantly different between placebo and thiopurines [86% vs. 69%; RR: 0.81; 95% CI: 0.64–1.02]. **Serious AEs** were reported in two trials[30,51] including 125 patients; 13.5% of those receiving AZA versus 3.8% of those receiving placebo developed **serious AEs** [pooled RR: 2.57; 95% CI: 0.92–7.13]. The quality of evidence was deemed low due to a very low number of events [n = 19] and wide confidence intervals.

One study reported on a validated **quality of life** measure [IBDQ][51]. The greatest difference between groups was observed at week 4 [43% for AZA and 30% for placebo]. Regarding **biochemical improvement**, only some of the trials reported on changes at the end of the induction period; no dichotomous data were available that allowed for a pooled

analysis calculation. Overall, most trials reported no differences in **biomarkers** of inflammation such as erythrocyte sedimentation rate [ESR], CRP, or orosomucoid in those receiving thiopurines as compared with placebo[48,52-54]. Reinisch *et al.*[51] reported a similar proportion of elevated faecal calprotectin at baseline and at weeks 4 and 12 for the thiopurines and placebo groups. Candy *et al.*[47] reported a slight increase of ESR in the group receiving placebo and prednisolone versus a statistically significant decrease in ESR in those receiving AZA and prednisone.

Methotrexate

Only one relevant placebo-controlled RCT was retrieved. In this study[55], 141 steroid-dependent patients with active CD were randomized to either 25 mg/week of intramuscular MTX or placebo for 16 weeks with a concomitant daily dose of prednisolone [20 mg at initiation] that was reduced over a 3-month period [Supplementary Material, SoF Table 6]. After 16 weeks, a significantly larger proportion of patients treated with MTX were in **clinical remission** than placebo [RR: 2.06; 95% CI: 1.09–3.89]. The rate of treatment discontinuation for **AEs** [mainly liver enzyme elevations and nausea] was significantly higher in comparison with placebo [RR: 8.00; 95% CI: 1.09–58.51]. However, this study is strongly limited by imprecision and some confounding factors, such as the concomitant use of steroids. No studies were found that compared MTX monotherapy versus placebo for the **induction of remission** of moderate-to-severe CD. No agreement was achieved in the Consensus regarding the use of MTX for inducing CD remission and therefore the Consensus decided to make no recommendation.

Three small and heterogeneous studies compared the efficacy of MTX and thiopurines for induction of **remission** in CD[56-60] [Supplementary Material, SoF Table 7]. These studies used different dosages and routes of administration. Two studies used oral MTX at doses of 16 mg/week[59] and 12.5 mg/week[56], and one used intravenous [IV] MTX at 25 mg/week[60]. All patients were steroid-dependent and received systemic steroids at inclusion. None of the individual studies or the pooled analysis demonstrated a significant difference in the likelihood to achieve **remission** [RR: 0.87; 95% CI: 0.70–1.09] [Supplementary Figure 12]. Although the risk of **AEs** is higher with MTX, the data are very sparse and the quality of evidence is very low for both outcomes. Accordingly, no recommendation can be made.

Based on the current evidence, agreement on a recommendation for the use of MTX for inducing clinical remission in patients with CD could not be reached. However, MTX may be considered as an option for steroid-dependent patients with moderate-to-severe disease when alternative options [including surgery] cannot be used. The need to stop therapy in patients planning a pregnancy must be considered[61].

Monoclonal antibodies

Recommendation 1.5. ECCO CD Treatment GL [2019]

We recommend the use of TNF inhibitors (infliximab, adalimumab, and certolizumab pegol) to induce remission in patients with moderate-to-severe Crohn's disease who have not responded to conventional therapy (strong recommendation, moderate-quality evidence).

Monoclonal antibodies directed against TNF-α are fast-acting and potent anti-inflammatory agents. Anti-TNF therapies approved for the treatment of CD include infliximab, adalimumab, and certolizumab pegol [the latter is not approved in the European Union for CD, but is commercially available in Switzerland and Russia]. Infliximab is a chimeric mouse-human IgG1 monoclonal antibody administered intravenously at a dose of 5 mg/kg at 0, 2, and 6 weeks during induction and every 8 weeks thereafter. Adalimumab is a fully humanized IgG1 monoclonal antibody given subcutaneously (SC) at a dose of 160 mg and then 80 mg 2 weeks after induction, followed by 40 mg SC every 2 weeks.

Certolizumab pegol is a PEGylated Fab fragment against TNF-α self-administered SC at a dose of 400 mg at weeks 0, 2, and 4, followed by 400 mg every 4 weeks thereafter.

Data on anti-TNF agents versus placebo [infliximab, adalimumab, and certolizumab pegol] from several meta-analyses of RCTs[62-64] support their efficacy for induction of **clinical remission** [RR: 1.6; 95% CI: 1.17–2.36] and **clinical response** [RR: 1.43; 95% CI: 1.17–1.73] [Supplementary Material, SoF Table 8] in patients who did not achieve adequate response or were intolerant to corticosteroids and/or immunosuppressants. Limited endoscopic data were available for the induction period; two studies showed a non-significant trend towards enhanced mucosal healing [RR: 3.25; 95% CI: 0.53–19.8][65,66]. However, the evidence was downgraded due to imprecision. Data on **clinical remission** were highly heterogeneous [I^2 = 63%], while data on **endoscopic improvement** were affected by high imprecision due to the low number of patients included in the meta-analysis [n = 35]. Data on **PRO response** and **remission**, **biochemical** and **radiologic improvement**, and **quality of life** are insufficient. There was no difference in terms of **AEs** [RR: 0.99; 95% CI: 0.90–1.08].

The choice of anti-TNF agent depends on patient preference, availability, cost, and accessibility. However, in a 2015 network meta-analysis, pairwise comparison revealed that infliximab with AZA [OR: 3.1; 95% CI: 1.4–7.7] and adalimumab monotherapy [OR: 2.1; 95% CI: 1–4.6] were superior to certolizumab pegol for **induction of remission**[67].

The timing of introduction of biologic agents is a matter of debate. It has been suggested that patients presenting with poor prognostic factors [e.g. fistulizing perianal disease, extensive disease, deep ulcerations, complicated phenotype] would benefit from the early introduction of anti-TNF to achieve a reduced risk of surgery, hospitalization, or development of disease-related complications[15]. Furthermore, anti-TNF agents might be more effective if introduced earlier [in the first 2 years] in disease course[68-72], although these results are based on post-hoc analyses from clinical trials.

Recommendation 1.6. ECCO CD Treatment GL [2019]

We suggest against the combination of adalimumab and thiopurines over adalimumab alone to achieve clinical remission and response (weak recommendation, moderate-quality evidence).

Only one RCT [the DIAMOND trial][73] studied the use of combination therapy of adalimumab with thiopurine as compared with adalimumab monotherapy for the induction of **clinical remission** in patients naïve to both therapies [Supplementary Material, SoF Table 9]. In this trial, combination therapy was not superior to adalimumab monotherapy for inducing **clinical remission** [RR: 0.95; 95% CI: 0.78–1.15]. However, combination therapy was associated with endoscopic improvement at week 26 [RR: 1.32; 95% CI: 1.06–1.65], although this benefit was lost at the end of 1 year. There was no increase in **AEs** leading to discontinuation associated with combination therapy [RR: 1.03; 95% CI: 0.60–1.78]. Of note, the dose of AZA used in this trial was lower than the usual dose used in CD patients [25–100 mg/day instead of 2–2.5 mg/kg/day].

Recommendation 1.7. ECCO CD Treatment GL [2019]

We recommend combination therapy with a thiopurine when starting infliximab to induce remission in patients with moderate-to-severe Crohn's disease who have had an inadequate response to conventional therapy (strong recommendation, moderate-quality evidence).

The SONIC [*Study Of Biologic and Immunomodulator Naive Patients In Crohn's Disease*] RCT[74] compared the efficacy of infliximab combined with AZA over infliximab monotherapy in patients naïve to both therapies and who failed to respond to steroids or 5-ASA [Supplementary Material, SoF Table 10]. Combination therapy resulted in higher

rates of **clinical remission at week 26** as compared with infliximab monotherapy [RR: 1.64; 95% CI: 1.07–2.53]. Combination therapy was also more likely to result in **mucosal healing** at this timepoint [RR: 1.82; 95% CI: 1.01–3.26]. There was no difference in **AEs** for those receiving combination therapy. Rather, there were significantly lower rates of **serious AEs** in those receiving combination therapy [RR: 0.56; 95% CI: 0.32–0.97].

A commonly encountered scenario in clinical practice is patients who have failed or have had an inadequate response to thiopurines and in whom anti-TNF therapy is planned. No RCT has directly compared whether in such cases thiopurine maintenance in combination with the anti-TNF would carry additional benefits in terms of efficacy. A post-hoc analysis of RCTs has shown no added benefit of the continued use of immunomodulator therapy after starting anti-TNF therapy in this setting[75]. However, immunogenicity should be considered and in the absence of direct evidence, an individualized approach should be considered[75].

Recommendation 1.8. ECCO CD Treatment GL [2019]

We recommend ustekinumab for induction of remission in patients with moderate-to-severe active luminal Crohn's disease with inadequate response to conventional therapy and/or to anti-TNF therapy (strong recommendation, high-quality evidence).

Ustekinumab is a IgG1 monoclonal antibody that binds to the p40 subunit shared by the pro-inflammatory interleukins 12 and 23[76]. In CD, induction should be given IV using a weight-based regimen of approximately 6 mg/kg[76,77]. One systematic review and meta-analysis pooled the results from RCTs in which ustekinumab was compared to placebo for **induction of remission** in patients with moderate-to-severe active luminal CD[78][Supplementary Material, SoF Table 11]. Four trials[77,79-81] involving 1947 patients treated with different ustekinumab intravenous doses or equivalent placebo reported **induction of clinical response** and **induction of clinical remission** at week 6. Data were extracted and a meta-analysis was performed, yielding a RR of obtaining **clinical response** of 1.56 [95% CI: 1.38–1.77] versus placebo [Supplementary Figure 13]. The quality of evidence was high. The RR of obtaining **clinical remission** was 1.76 [95% CI: 1.40–2.22] [Supplementary Figure 14]. The quality of evidence was high. An endoscopic substudy involving 252 CD patients revealed that 47.7% of patients receiving ustekinumab achieved **endoscopic improvement** at 8 weeks as compared with 29.9% of those receiving placebo [RR: 1.60; 95% CI: 1.13–2.26]. The quality of evidence was moderate. Four trials[77,79-81] reported on **AEs** [2024 patients] or **serious AEs** [1947 patients] after induction. The pooled RR of **any AEs** was not significantly different between ustekinumab and placebo [62.0% vs. 63.9%; RR: 0.96; 95% CI: 0.90–1.03] [Supplementary Figure 15]. Similarly, the pooled RR of any **serious AEs** was not significantly different between ustekinumab and placebo [5.2% vs. 6.4%; RR: 0.79; 95% CI: 0.54–1.15] [Supplementary Figure 16]; the quality of evidence was high. The rate of antibody drug formation seems to be low [under 5%][82].

Recommendation 1.9. ECCO CD Treatment GL [2019]

We recommend vedolizumab for induction of response and remission in patients with moderate-to-severe Crohn's disease with inadequate response to conventional therapy and/or to anti-TNF therapy. (strong recommendation, moderate-quality evidence).

Vedolizumab is a monoclonal IgG1 antibody that acts by blocking the α4β7 integrin resulting in gut-selective anti-inflammatory activity[83]. It is administered intravenously at a fixed dose of 300 mg at 0, 2, and 6 weeks for induction, and every 8 weeks thereafter. Patients who do not achieve response at week 6 can benefit from an additional administration at week 10[84]. Three randomized trials involving 969 patients treated with vedolizumab or placebo reported on induction

of **clinical response**, induction of **clinical remission**, and **serious AEs** in adult patients with moderate-to-severe active CD[83,85,86][Supplementary Material, SoF Table 12]. Patients in these studies were followed up for 6 to 10 weeks. **Clinical remission** was more common in patients receiving vedolizumab compared with placebo [RR: 2.01; 95% CI: 1.50–2.71] [Supplementary Figure 17]. Likewise, **clinical response** was also more common in patients receiving vedolizumab compared with placebo [40.8% vs. 25.7%; RR: 1.55; 95% CI: 1.14–2.11] [Supplementary Figure 18]. The quality of evidence for these outcomes was high. Rates of **serious AEs** with vedolizumab were not significantly different to placebo [RR: 0.94; 95% CI: 0.61-1.45] [Supplementary Figure 19]. The quality of evidence for this outcome was moderate due to serious imprecision arising from sparse data.

Recommendation 1.10. ECCO CD Treatment GL [2019]

We equally suggest the use of either ustekinumab or vedolizumab for the treatment of moderate-to-severe active luminal Crohn's disease in patients who have previously failed anti-TNF therapy (weak recommendation, very low-quality evidence).

One systematic review and meta-analysis performed an indirect comparison of ustekinumab and vedolizumab for **induction of remission** in patients with moderate-to-severe active luminal CD who were non-responsive or intolerant to previous anti-TNF agents[87].

Four trials[77,80,83,86] involving a total of 1249 patients treated with ustekinumab or vedolizumab reported on induction of **clinical response** and **clinical remission** [Supplementary Material, SoF Table 13]. The pooled RR of **clinical response** [35.8% vs. 33.1%; RR:1.14; 95% CI: 0.65–1.99] and **clinical remission** [16.3% vs. 13.3%, RR: 1.16; 95% CI: 0.54–2.48] were not significantly different between ustekinumab and vedolizumab, but the quality of evidence was very low for both outcomes.

Four trials[77,80,83,86] involving a total of 1541 patients treated with ustekinumab or vedolizumab reported on **AEs** or **serious AEs** after induction. The pooled RR of any **AEs** was not significantly different between ustekinumab and vedolizumab [64.2% vs. 56.2%; RR: 1.00; 95% CI: 0.82–1.23]. Finally, the pooled RR of any **serious AEs** was not significantly different between ustekinumab and vedolizumab [7.1% vs. 7.7%; RR: 0.95; 95% CI: 0.43–2.12]; the quality of evidence was very low. However, surgery should always be considered as an option in refractory patients.

Key points for clinical practice

Budesonide is effective for the **induction of remission** in patients with mild-to-moderate CD, defined as a CDAI between 150 and 220, and/or presence of mild lesions at endoscopy, or a Simple Endoscopic Score-CD [SES-CD] ≤ 6 or a Crohn's Disease Endoscopic Index of Severity [CDEIS] ≤ 8 with ileal and/or right colon involvement. 5-ASA compounds and sulphasalazine have no therapeutic effect. There is a knowledge gap on how to treat mild-to-moderate CD localized in different parts of the gastrointestinal tract other than the ileum and right colon or in patients with extensive disease. Therefore, the decision is left to the clinician, who should consider the patient's individual characteristics, prognostic factors, and cost/benefit ratios of therapies.

Although systemic steroids are effective in inducing remission in moderate-to-severe CD, they are limited by important side effects. Additionally, long-term use of corticosteroids does not prevent disease relapse[30,88]. Therefore, we suggest that the presence of corticosteroid dependency or excess [the inability to wean steroids below the equivalent of prednisolone 10 mg/day or budesonide 3 mg/day within 3 months of starting steroids, a relapse within 3 months of

stopping steroids, or the need for more than a single course of corticosteroids in 1 year] should all warrant a steroid-sparing strategy. Thiopurines alone are not effective in inducing remission. However, since thiopurines have a slow onset of action [8–12 weeks][43] and are effective for maintaining remission in steroid-dependent CD patients [see Maintenance section, Recommendation 2.2], they are frequently combined with steroids at the commencement of therapy. In patients with steroid dependency, a combination of steroids and MTX has limited efficacy in inducing remission at week 16 and is associated with a high risk of **AEs**. Therefore, this option may be considered only where other medical treatments and surgery are not indicated or are associated with some increased individual risks[89].

For patients with moderate-to-severe CD [usually defined as a CDAI > 220 and/or CDEIS > 8 or SES-CD > 6] with inadequate response or intolerance to conventional therapy [steroids and/or thiopurines], we recommend the use of monoclonal antibodies. These include anti-TNF agents [such as infliximab, adalimumab, and certolizumab pegol], ustekinumab, or vedolizumab. All these agents are effective both in biologic-naïve and -experienced CD populations. The choice depends on patient characteristics and preferences, costs, and local availability[8]. For the induction of remission, in treatment naïve patients, the combination of infliximab with thiopurines is more effective than infliximab alone for achieving steroid-free remission.[74] For adalimumab, no benefit of combination therapy over adalimumab alone was observed in the only RCT performed to date[73]. The SONIC trial[74] demonstrated the superiority of either infliximab alone or the combination of infliximab and AZA over AZA monotherapy or even in combination with steroids; this option should be considered and even preferred in steroid-dependent patients. The REACT [*Early combined immunosuppression for the management of Crohn's disease*] trial showed that the early use of monoclonal antibodies [adalimumab] combined with immunosuppressants in patients at high risk of complications, as compared to a more conventional step-wise management, was associated with significantly lower rates of complications and need for hospitalization and/or surgery in patients with early CD.[15] A prospective cohort study demonstrated that concomitant immunomodulator use is associated with lower immunogenicity to anti-TNF.[90] In clinical practice, the potential added efficacy benefit and lower immunogenicity of combination therapy needs to be balanced against a potential increase in **AEs** in the long term[91,92]. Combination therapy does not seem to be associated with safety concerns, at least in the short term. However, a large nationwide cohort study showed that combination therapy is associated with higher risk for lymphoma and serious infection, as compared to Anti-TNF monotherapy. [91,92] Therefore, the decision is left to the clinician, who should consider patient characteristics, costs, risks, and local regulations. Importantly, risk needs to be individualized, as specific patient groups, such as the elderly, maybe at higher risk for infections or lymphoma, while young male maybe at higher risk for specific complications, such as hepatosplenic T-cell lymphoma[93,94].

In patients who fail anti-TNF therapy, ustekinumab or vedolizumab are indicated. There is currently no direct evidence on the comparison between vedolizumab versus anti-TNF and ustekinumab versus anti-TNF in patients treated either with vedolizumab or ustekinumab as a first biologic. No RCTS have specifically assessed the efficacy and safety of these agents when used in combination therapy as compared to monotherapy; however overall immunogenicity rates seem to be low; besides, in the originator trials, no difference in efficacy was observed in those patients treated concomitantly with immunomodulator. However, in patients with moderate-to-severe CD with limited disease extent or refractory to at least one monoclonal antibody, surgery should always be considered as an alternative option.

While RCTs evaluate the efficacy of a drug for **induction of remission** and thereafter for **maintaining remission** using validated indices of clinical activity, the clinician usually bases his or her choice of first line-therapy not only on symptoms but also on the perceived disease severity [the impact of disease in the individual patient, the cumulative complications and surgical resections, risk factors for complications, the inflammatory burden of disease, and disease course][1].

Therefore, appropriate studies that address the early use of biologics over a step-wise approach, focusing on the prevention of complications and disease-modification outcomes, and that validate risk factors for disease progression [age, extensive disease, upper tract involvement] should be performed. Such studies were identified by this Consensus as very important research gaps.

Section 2. MAINTENANCE OF REMISSION

5-ASA

Recommendation 2.1. ECCO CD Treatment GL [2019]

We recommend against the use of oral 5-aminosalicylic acid for maintenance of medically induced remission in patients with Crohn's disease (strong recommendation, low-quality evidence).

Oral 5-ASA compounds have been extensively studied for the maintenance of medically induced **remission** of CD [Supplementary Material, SoF Table 14]. No statistically significant benefit has been demonstrated [RR: 1.03; 95% CI: 0.92–1.16] [Supplementary Figure 20]. Overall, 11 placebo-controlled trials that assessed doses between 1 and 4 g/day were identified. Treatment durations ranged from 4 months to 36 months, with most trials evaluating a 12-month duration of therapy.[95] There were no significant differences in the proportion of patients experiencing an **AE**, or withdrawing due to **AEs** or **serious AEs** [RR: 1.93; 95% CI: 0.18–21.1]. The safety data were very sparse [3 events] and considerably limited this conclusion [Supplementary Figure 21].

Immunosuppressants

Thiopurines

Recommendation 2.2. ECCO CD Treatment GL [2019]

Thiopurines are recommended for the maintenance of remission in patients with steroid-dependent Crohn's disease (strong recommendation, moderate-quality evidence).

The effect of maintenance treatment with AZA or MP administered to patients with CD who are steroid-dependent has been investigated in one meta-analysis[96] [Supplementary Material, SoF Table 15]. This meta-analysis included data from six trials published between 1971 and 2013[30,47,53,97-100]. A total of 489 patients treated with AZA [1.0 to 2.5 mg/kg/day] were included and followed for 6 to 18 months. **Clinical remission** was defined according to different criteria [CDAI in 3, DAS score in 2; others, 1]. AZA was superior to placebo for the **maintenance of remission** in steroid-dependent patients [RR: 1.19; 95% CI: 1.05–1.34].

Safety outcomes were reported in four trials published between 1978 and 2013[30,97-99], including a total of 556 patients followed for 6 to 18 months. The overall risk of inducing **serious AEs** during maintenance treatment with thiopurines was significantly higher than with placebo [RR: 2.45; 95% CI: 1.22–4.90]. The rate of **serious AEs** reported in patients treated with thiopurines versus placebo was 9.0% [22/245] versus 2.9% [9/311]. Pancreatitis, leukopenia, nausea, allergic reaction, and infections were the most frequent **serious AEs**.

Recommendation 2.3. ECCO CD Treatment GL [2019]

We recommend against the early introduction of thiopurine therapy in patients with newly diagnosed Crohn's disease for maintaining remission (weak recommendation, low-quality evidence)

It has been hypothesized that the early introduction of thiopurines could modify disease course. Two studies have evaluated the efficacy of early use of thiopurines: the AZTEC [*AZathioprine for Treatment of Early Crohn's disease in adults*][99] and the RAPID [*Résultat de l'Adjonction Précoce d'ImmunoDépresseurs*][101] trials [Supplementary Material, SoF Table 16]. The latter has been excluded from our SoF table because it was not conducted against placebo or no treatment. In the AZTEC study, adult patients with a recent [< 8 weeks] diagnosis of uncomplicated CD were randomized

to receive either AZA or placebo up to week 76. Only corticosteroids were allowed to treat active disease in this study population. The results were not statistically significant for any of the critical outcomes evaluated. After 76 weeks of treatment, **clinical remission** did not differ between the two groups [RR: 1.27; 95% CI: 0.94–1.72]; 30 patients treated with AZA [44.1%] and 23 given placebo [36.5%] were in sustained **corticosteroid-free remission** [RR: 1.21; 95% CI: 0.79–1.84]. The rates of relapse [defined as CDAI score > 175] and corticosteroid requirements were similar between groups. **Serious AEs** occurred in 14 patients [20.6%] in the AZA group and 7 [11.1%] in the placebo group [RR: 1.85; 95% CI: 0.8–4.29].

Methotrexate

Recommendation 2.4. ECCO CD Treatment GL [2019]

We recommend methotrexate administered parenterally for the maintenance of remission in patients with steroid-dependent Crohn's disease (weak recommendation, moderate-quality evidence).

Data on the use of parenterally administered MTX is derived from one double-blind, placebo-controlled RCT[55] where patients were administered weekly intramuscular injections of 15 mg MTX or placebo of identical appearance for 40 weeks [Supplementary Material, SoF Table 17]. Patients with previously active CD who had entered **remission** after 16 to 24 weeks of treatment with 25 mg MTX given intramuscularly once weekly were randomly assigned to receive either MTX at a dose of 15 mg intramuscularly once weekly or placebo for 40 weeks. No other treatments for CD were permitted. After 40 weeks, the proportion of patients who remained in **remission** was higher in the MTX group than in the placebo group [65% vs 39 %; RR: 1.67; 95% CI: 1.05–2.67]. Fewer than 50% of the patients in the MTX group had relapsed by the end of the study.

There were no differences in severe **AEs** in the MTX group [n = 40] as compared with the placebo group [n = 36] over the 40-week observational period [one patient had cervical dysplasia and the other had a viral respiratory tract infection]. Nausea and vomiting occurred more frequently among patients in the MTX group [40% vs 25% in the placebo group]. Although none of the symptoms were severe, one patient discontinued treatment because of these symptoms. No patient had leukopenia of sufficient severity to require withholding treatment or withdrawal from the study. The overall incidence of **AEs** was similar in both groups.

Monoclonal antibodies

Recommendation 2.5. ECCO CD Treatment GL [2019]

In patients with Crohn's disease who achieved remission with anti-TNF agents, maintenance treatment using the same treatment is recommended (strong recommendation, moderate-quality evidence).

Two systematic reviews analysed the effect of maintenance treatment with anti-TNFs [infliximab, adalimumab, and certolizumab pegol] administered to patients with CD who had achieved disease **remission** with the same anti-TNF drug[62,63] [Supplementary Material, SoF Table 18]. Five landmark trials published between 2002 and 2007[102-106] were pooled in the meta-analysis from Stidham *et al.*[62]; one study was on infliximab, two on adalimumab, and two on certolizumab pegol. A total of 1771 patients were included and followed for 24 to 30 weeks. Four of the five studies included primary responders only, while one study included all subjects. **Clinical remission** was defined as a CDAI score < 150. The overall likelihood of maintaining **remission** with anti-TNFs versus placebo was 1.78 [95% CI: 1.51–2.09]. The following values were achieved with infliximab: 1.86 [95% CI: 1.21–2.86]; adalimumab: 2.06 [95% CI: 1.59–2.82];

and certolizumab pegol: 1.62 [95% CI: 1.30–2.02]. A network meta-analysis[62] found no statistically significant differences between the three agents.

There is no pooled data available on **serious AEs** of all anti-TNFs against placebo. In a network analysis performed in the framework of a Cochrane collaboration,[107] the dose-adjusted ORs [95% CI] for **SAEs** for adalimumab, infliximab, and certolizumab pegol were 1.01 [0.64–1.59], 1.13 [0.79–1.62] and 1.57 [0.96–2.57], respectively. Thus, monotherapy with anti-TNFs is considered safe as compared with placebo for the **maintenance of remission** in CD patients, although the relatively small sample size and short follow-up of RCTs do not allow the detection of **AEs** that may appear in larger and longer observational studies.

Recommendation 2.6. ECCO CD Treatment GL [2019]

We recommend vedolizumab for maintaining clinical remission in patients with moderate-to-severe Crohn's disease who achieved remission with vedolizumab (strong recommendation, moderate-quality evidence).

Vedolizumab monotherapy, given IV at 300 mg every 8 weeks, was superior to placebo in maintaining **clinical remission** in patients with moderate-to-severe CD who achieved **remission** with vedolizumab [RR: 1.81; 95% CI: 1.26–2.59] [Supplementary Material, SoF Table 19]. At week 52, 60/154 patients [39.0%] receiving vedolizumab every 8 weeks and 56/154 patients [36.4%] receiving vedolizumab every 4 weeks were in **clinical remission** as compared with 33/153 patients [21.6%] receiving placebo [$p < 0.001$ and $p = 0.004$, respectively]. Moreover, vedolizumab was effective at maintaining **steroid-free clinical remission** [RR: 2.00; 95% CI: 1.11–3.61] and showed a similar incidence of **AEs** compared with placebo through week 54 [RR: 1.21; 95% CI: 0.73–2.00][83]. Longer-term data beyond 52 weeks are required to correctly evaluate the **safety** profile.

Recommendation 2.7. ECCO CD Treatment GL [2019]

We recommend the use of ustekinumab to maintain clinical remission in patients with Crohn's disease who achieved remission with ustekinumab (strong recommendation, moderate-quality evidence).

One RCT reported outcomes for the **maintenance of remission** with ustekinumab in CD patients [Supplementary Material, SoF Table 20][80]. Patients responding to ustekinumab in the induction period were re-randomized to receive ustekinumab every 8 or 12 weeks or placebo. Over a 44-week period, 51% of the patients receiving SC ustekinumab were in **clinical remission** as compared with 35.9% of those receiving placebo [RR: 1.42; 95% CI: 1.10–1.84]. A subgroup analysis demonstrated that at week 44, **clinical remission** was achieved by 53.1% in patients receiving ustekinumab every 8 weeks and by 48.8% in patients receiving ustekinumab every 12 weeks as compared with 35.9% in the placebo group. The difference between treatment every 8 weeks and placebo was 17.2% [95% CI: 5.3–29.2] and was 13% between treatment every 12 weeks and placebo [95% CI: 1.1–24.9]. Therefore, there was no difference between ustekinumab administered every 8 or 12 weeks. At 44 weeks, **corticosteroid-free remission** was achieved in 29.8% of patients receiving placebo versus 44.7% of patients receiving ustekinumab [RR: 1.50; 95% CI: 1.12–2.02]. The pooled RR of any **AEs** was not significantly different between patients that were given placebo and those administered ustekinumab [15.0% vs. 11.0%; RR: 0.73; 95% CI: 0.43–1.25].

There is limited data on **endoscopic remission** as this was assessed in a subgroup analysis of 70 patients [46 ustekinumab vs. 24 placebo] at 44 weeks. There was no statistically significant difference in **endoscopic remission** between patients in the placebo group as compared with patients in the treatment arm [RR: 2.61; 95% CI: 0.32–21.08].

There were no deaths during the 44 weeks of maintenance. Common **AEs** were headache, nausea, and arthralgia, with no significant difference in occurrence between the ustekinumab and placebo group. There was an identical occurrence of non-melanoma skin cancers in the maintenance group [n=4 patients in placebo and ustekinumab group]. Longer-term data beyond 52 weeks is required to correctly evaluate the safety profile.

There are no randomized head-to-head trials comparing vedolizumab or ustekinumab to anti-TNF agents for the maintenance of **clinical remission** in patients with moderate-to-severe CD who have achieved response or remission with the same agent. A network meta-analysis[108] included nine RCTs [all trials used CDAI to define **clinical remission**] with varying follow-up times. The certolizumab pegol trial had a follow-up time of only 26 weeks. All comparisons were indirect [through the placebo, the "common comparator"]. Therefore, the quality of evidence was very low. No specific agent was safer than the others in the maintenance phase. Based on efficacy data, there is no evidence to support switching to vedolizumab or ustekinumab in patients who responded to induction treatment with any anti-TNF, or, vice-versa. There is a clear need to identify biomarkers that could guide therapeutic choices and to conduct appropriately sized head-to-head trials that could allow for the identification of patient subgroups that would benefit from a given biologic over the other.

Maintenance Strategies

Recommendation 2.8. ECCO CD Treatment GL [2019]

In Crohn's disease patients in clinical remission under anti-TNF treatment, there is currently insufficient evidence to recommend for or against the use of proactive therapeutic drug monitoring to improve clinical outcomes as compared to routine care (weak recommendation, moderate-quality evidence).

Data from two RCTs with a total of 395 patients with CD were used to support this recommendation [Supplementary Material, SoF Table 21]. These two RCTs showed no advantage of therapeutic drug monitoring [TDM] over clinically based anti-TNF dosing for any of our critical outcomes, namely **clinical remission** [1 study; 62.6% vs. 54.9%; RR: 1.14; 95% CI: 0.89–1.47], **steroid-free clinical remission** [1 study; 30.5% vs. 40.0%; RR: 0.76; 95% CI: 0.46–1.26], **endoscopic remission** [1 study; 51.2% vs. 52.5%; RR: 0.98; 95% CI: 0.68–1.40], **biochemical remission** [62.6% vs. 54.9%; RR: 1.14; 95% CI: 0.89–1.47], or **serious AEs** [1 study; 34.1% vs. 27.5%; RR: 1.24; 95% CI: 0.68–2.23][109,110].

In the TAXIT trial, a total of 273 IBD patients with stable response to maintenance infliximab therapy were randomised either to concentration- or clinical-based infliximab dosing. Both groups were dose-optimized or dose-reduced to achieve a baseline trough level between 3 to 7 μg/mL. This dose-optimization phase of the study showed that in patients in clinical remission, a trough level < 3 μg/mL or > 7 μg/mL was observed in 29% and 27% of patients, respectively. No differences in **clinical** or **biochemical remission** at 1 year were observed between clinical- [66%] and proactive TDM- [69%] based groups[109]. Nevertheless, the group that received proactive monitoring had fewer relapses during follow-up [7% versus 17%, $p = 0.018$].

In the TAILORIX trial, 122 biologically naïve patients with CD treated with an induction combination therapy with infliximab and immunosuppressant were randomised after 14 weeks to the following three groups: dose

intensification based on clinical features, biomarkers, and trough levels of infliximab, with optimization steps of 2.5 mg/kg [TDM1] or 5 mg/kg [TDM2] or dose intensification based on clinical features alone [control group][110]. The infliximab dose was adapted to maintain a trough level > 3 µg/mL. There was no difference in sustained **steroid-free clinical remission** with **mucosal healing** [CDAI < 150 from week 22 to 54] in the three randomization arms [33% in TDM1; 27% in TDM2; 40% in control; $p = 0.50$].

Both studies have important limitations in their study designs[109,110], which collectively have lowered the strength of our recommendation. While the outcomes in both studies were **clinical remission**, other important issues, such as costs and immunogenicity, also need to be considered. The prospective cohort study PANTS [*Personalised anti-TNF therapy in Crohn's disease study*] showed that anti-TNF failure is highly dependent on low drug concentrations and immunogenicity, and that dose intensification, especially during the induction period, may improve outcomes and treatment success.[90] Therefore, the Consensus believes that large, well-powered prospective RCTs with adequate stratification of patients are still required.

Recommendation 2.9. ECCO CD Treatment GL [2019]

In Crohn's disease patients that have lost response to an anti-TNF agent, there is currently insufficient evidence to recommend for or against the use of reactive therapeutic drug monitoring to improve clinical outcomes (weak recommendation, low-quality evidence).

Reactive TDM refers to the practice of measuring anti-TNF trough level drug concentration and/or ADA in patients on anti-TNF therapy with active disease to elucidate the mechanism of loss of response [LOR] and to guide clinical decision making. Reactive TDM was compared to empiric IFX optimization [based on clinical judgment alone] in only one randomised, controlled, single-blind, multicentre study in a cohort of 69 patients with CD with secondary IFX failure[111]. Patients were randomised to IFX dose intensification [5 mg/kg every 4 weeks; n = 36] or interventions based on serum IFX and IFX ADA levels using the proposed algorithm [n = 33]. There was no difference in regaining **clinical response** between the TDM-based group [19/33, 57.6%] and the symptom-based group [19/36, 52.8%] [RR: 1.09; 95% CI: 0.71-1.67; $p = 0.81$] [Supplementary Material, SoF Table 22].

However, numerous studies have shown a positive association between adequate drug concentration and various clinical outcomes from **clinical response** to **mucosal healing**. Based on these observational data, recent clinical practice guidelines and a group of 25 international experts supported the use of reactive TDM, despite recognising the very low quality of evidence[112,113]. Supporting evidence comes from case-control observational studies[114,115]. In a retrospective study of 312 patients with endoscopically active IBD treated with IFX who underwent dose escalation, TDM-based [n = 149] and clinical decision-based [n = 163] cohorts were compared for **endoscopic remission** and CRP at a median of 6 months after adjustment. Post-adjustment, **endoscopic remission** was observed in 63% of patients in the TDM cohort as compared with 48% in the non-TDM cohort [$p = 0.05$]; **clinical response** was observed in 69% versus 57%. [$p = 0.01$] and there fewer hospitalisations in the TDM group [22% TDM vs. 35% non-TDM; $p = 0.025$][114]. In another study, a modified version of the Steenholdt optimization algorithm[115], using a cut-off of 3 µg/ml, was applied to a prospective cohort. **Clinical response** at 12 weeks was compared between this group and a retrospective control group, in which dosing decisions were made independently of TDM results. There was no significant difference in clinical outcomes[115], but the TDM approach was significantly more cost-effective [> 10% decrease in costs]. Therefore, the existing limited evidence does not support an association between a reactive TDM strategy and superior clinical outcomes but does suggest a cost savings benefit even after considering biosimilar use.[116]

Recommendation 2.10. ECCO CD Treatment GL [2019]

We suggest continuation of thiopurines in Crohn's disease patients in long-term remission on thiopurine maintenance therapy as the risk of relapse is higher when the treatment is discontinued (weak recommendation, low-quality evidence).

We conducted our own meta-analysis to compare the two strategies [i.e. cessation vs. continuation of treatment] in 215 CD patients in long-term **remission** on thiopurine maintenance therapy [Supplementary Material, SoF Table 23]. Data from four trials were included[97,117-120]. Patients included received AZA from 6 to 42 months before being randomized to continue or stop AZA[118] or to continue AZA or placebo[97,117,119]. All studies had a follow-up time of 12 to 18 months. Our results revealed that the RR of **clinical relapse** is 2.39 [95% CI: 1.38–4.13] [Supplementary Figure 22]. Our meta-analysis effect estimate for **serious AEs** was RR 0.32 [95% CI: 0.04–2.92]. Although the data showed a trend towards fewer **serious AEs** occurring with discontinuation of treatment, the results were not statistically significant [Supplementary Figure 23]. However, regular assessment for the long-term risks/benefits should be performed considering the long-term safety data from the population base. To summarize, the evidence for the **prevention of clinical relapse** is in favour of continuation of treatment, as significantly more relapses occurred when the treatment was discontinued while the risk of **SAEs** was not different between AZA and placebo/no treatment. Data from studies that compared patients receiving AZA versus placebo/no treatment for more than 18 months are lacking and this represents an important research gap. Data from observational population studies suggest caution and regular monitoring, especially for the risk of non-melanoma skin cancer and lymphoma in patients exposed to long-term treatment with thiopurines[20]; the limited follow-up time and the number of patients included in the studies of the meta-analysis are unable to capture **AEs** and **serious AEs** that may occur in the long-term.

We also reviewed the literature to compare the approach of using long-term, low-dose thiopurines versus drug discontinuation. After an exhaustive literature search, we did not find evidence comparing the two treatment strategies. Only one trial was identified where dose reduction of thiopurines was compared to discontinuing thiopurines in the setting of combination therapy in patients with IBD. The information was incomplete as it was not possible to separate data from ulcerative colitis and CD patients[121]. Therefore, no specific recommendation was made.

Recommendation 2.11. ECCO CD Treatment GL [2019]

In patients with Crohn's disease who have achieved long-term remission with the combination of infliximab and immunosuppressants, we suggest monotherapy with infliximab (weak recommendation, very low-quality evidence).

A Cochrane review[120] based on two RCTs[121,122] revealed the same relapse rate among patients who continued combination therapy with AZA [27/56; 48%] or infliximab monotherapy [27/55; 49%] [RR: 1.02; 95% CI: 0.68–1.52] [Supplementary Material, SoF Table 24]. The same meta-analysis[120] analysed the rates of **AEs** for infliximab versus combination therapy [RR:1.11; 95% CI: 0.44–2.81; very low quality evidence] or **serious AEs** [RR: 1.00; 95% CI: 0.21–4.66; very low quality evidence]. These results are rather uncertain due to an unclear risk of bias. Common **AEs** in the combination therapy studies included infections, elevated liver values, arthralgia, and infusion reactions. For some infrequent **AEs**, longer follow-up studies [> 12 months] are necessary to correctly evaluate the safety profile. A higher risk of lymphoma exists when anti-TNF agents are combined with conventional immunosuppression. However, the absolute rates remain very low [3.23, 95% CI 1.5-6.9] and were estimated as 1.9 per 10 000 patient-years in one meta-analysis consisting of almost 9000 patients included in the SEER database[123].

Recommendation 2.12. ECCO CD Treatment GL [2019]

In patients with Crohn's disease who have achieved long-term remission with the combination of adalimumab and immunosuppressants, we suggest monotherapy with adalimumab (weak recommendation, low-quality evidence).

On the basis of a meta-analysis of nine studies on adalimumab by Chalhoub *et al.*[124], the data included were re-analysed because the intervention and control groups had to be reversed to match the relevant PICO question. The result of this recalculation did not reveal any differences in maintenance of **clinical remission** [RR: 1.01; 95% CI: 0.91–1.13] between combination therapy and monotherapy [Supplementary Material, SoF Table 25 and Supplementary Figure 24]. Whereas this meta-analysis was limited to 1 year of follow-up [week 56] in the sensitivity analysis, studies with a longer follow-up [> 52 weeks] showed similar results. There is no quality data available for **steroid-free clinical remission**. However, in the ADHERE cohort, which is an open-label extension study that prospectively follows up the cohort of patients originally enrolled in the CHARM study on adalimumab[102], the rates of **steroid-free remission** were similar in patients with or without concomitant immunosuppression at baseline after 3 years of follow-up.[125] The meta-analysis by Chalhoub *et al.*[124] which was re-calculated, did not show any differences in **serious AEs** between monotherapy with adalimumab and combination therapy [RR: 0.88; 95% CI: 0.62–1.26] [Supplementary Figure 25].

Recommendation 2.13. ECCO CD Treatment GL [2019]

There is insufficient evidence to recommend either continuation or withdrawal of anti-TNF therapy in Crohn's disease patients after achieving long-term remission. Therefore, the decision to continue anti-TNF therapy should be individualized and potential consequences (risks and benefits) should always be discussed with the patient.

Currently, no randomized controlled study data regarding the withdrawal of anti-TNF therapy in CD patients with inactive disease are available[126]. This is true for anti-TNF therapy as monotherapy or when used in a combination therapy regimen. Several observational studies investigated disease course in CD patients following withdrawal of anti-TNF therapy. A prospective study followed 115 patients with CD on combination therapy for at least one year who discontinued anti-TNF after being in steroid free clinical remission for at least 6 months. The relapse rates at 12 and 24 months were 43.9%±5.0% and 52.2%±5.2% respectively[74]. A systematic review and meta-analysis included 23 observational cohort studies of 920 CD patients and found an overall relapse rate of 44% [95% CI: 36–51%; follow-up range: 6–125 months][127]. Furthermore, the relapse rate was 38% [95% CI: 13–63%; 126 patients] at 6 months after discontinuation, 40% [95% CI: 33–48%; 813 patients] at 12 months, and 49% [95% CI: 31–68%; 228 patients; range of follow-up 28–125 months] at > 25 months. The meta-analysis included studies in children and patients with perianal disease.

Following the aforementioned meta-analysis, 10 observational cohort studies reported relapse rates in accordance with the findings of the meta-analysis[128-137]. Two of these studies represent extensions of studies included in the meta-analysis[134,135]. One study investigated the risk of relapse in patients treated with a combination of anti-TNF and an immunomodulator who discontinued either of the two drugs[137]. The study found no difference in **relapse rates** with regards to the withdrawn drug; that is, 17/55 patients [30.9%] on biological therapy withdrawal relapsed compared with 4/20 patients [20%] in which the immunomodulator was withdrawn [$p = 0.401$].

In conclusion, observational studies report that up to half of patients will experience a relapse within the following 12 months after withdrawal. However, in the absence of controlled studies, the evidence surrounding withdrawal of anti-TNF therapy in patients with long-term remission remains scarce and inconclusive. Hence, no

recommendation regarding anti-TNF therapy can be made. The management decision therefore lies with the clinician, who should carefully consider the patient's profile, values, and preferences and any resource implications[138].

Key points for clinical practice

Immunosuppressants and biological agents are the most effective therapies to maintain medically-induced **remission** in moderate-to-severe CD patients. Aminosalicylates and steroids are not recommended in this setting due to lack of efficacy and long-term risk of **serious AEs** [steroids]. For patients with mild disease, no data is available that suggests any specific treatment strategy; no therapy and tight monitoring may be considered in this patient population in the maintenance phase.

Our literature search and data analysis showed that immunosuppressants, such as thiopurines and MTX, are recommended to maintain **remission** in steroid-dependent patients. As discussed in the previous section, the role of adding MTX or thiopurines to steroids for the **induction of remission** is limited. However, after steroids are stopped, maintenance with thiopurines or MTX [administered parenterally] can be an appropriate strategy. The choice between the two drug classes depends on careful consideration of patient's individual characteristics and preferences, safety profile, and drug availability. There is low-quality evidence supporting the continuation of thiopurines for long-term **remission,** as studies that directly compared long-term treatment with AZA versus no treatment or placebo did not have follow-up times > 18 months. Clinicians should balance the increased risk of relapse with thiopurine discontinuation with the increased risk of **AEs**. Many observational studies have now reported an increased risk of lymphoma and skin cancer for patients treated with thiopurines.[139,140] Therefore, regular monitoring should be provided to patients continuing thiopurines in the long term. Given the increased risk of **AEs** due to thiopurines, monoclonal antibodies can also be considered in this particular group of patients.

For CD patients where medically-induced **remission** has been achieved by a biological agent-based strategy, the use of the same agent is recommended to maintain **remission**. There is high-quality evidence in favour of this approach for anti-TNF agents, vedolizumab, and ustekinumab. There is no evidence to support switching to a different monoclonal antibody after treatment induction with a monoclonal antibody that was successful. Longer-term data beyond 52 weeks are required to correctly evaluate the **safety** profile of monoclonal antibodies, as the relatively small sample size and short follow up of RCTs does not allow for detection of some **AEs**, particularly very rare **AEs**, which may appear in larger and longer observational studies.

The combination of an anti-TNF agent and thiopurines is effective and safe both for induction and for maintenance. The risk of lymphoma with infliximab and thiopurines remains very low but should be considered[19] and adequately addressed with the same screening and prevention and regular monitoring recommended for thiopurine therapy[19]. Therefore, when remission is achieved with combination therapy with anti-TNF agents, maintenance with the same biological agent in monotherapy can be suggested.

Routine strategies to monitor and optimize biological therapy in CD by a TDM approach are not supported by the available controlled evidence, although we recognize the limitations. There is no clear clinical benefit in favour of a proactive or reactive TDM approach from the current data. However, some recent data suggest that a reactive TDM approach can result in cost savings also in the era of biosimilars[116], potentially justifying the use of such an approach where TDM is available. TDM can at least be used to guide dose optimization.

There is currently no evidence to give any recommendation regarding dose reduction of thiopurines during maintenance and there is no evidence on the benefits of withdrawing or continuing biological agents in patients with

stable long-term remission due to the lack of controlled studies. As stated in our Consensus, the decision is left to the clinicians and should be individualized and discussed with the patient, carefully considering the risk of relapse, disease progression and development of complications, and the risks of potential side effects. The long-term management of patients in remission is therefore an important research gap.

SECTION 3. PERIANAL FISTULISING DISEASE

Therapeutic management of complex perianal fistulising disease

Recommendation 3.1. ECCO CD Treatment GL [2019]

We recommend infliximab for the induction and maintenance of remission in complex perianal fistulae in Crohn's disease (strong recommendation; low quality of evidence).

Infliximab was the first agent shown to be effective in an RCT for inducing closure of perianal fistulae and for maintaining this response over 1 year. Complete response [defined as the absence of any draining fistulae at two consecutive visits at least 4 weeks apart] was observed in 4/31 placebo patients [12.9%] versus 29/63 infliximab patients [46%] [RR: 3.57; 95% CI: 1.38–9.25[141]] [Supplementary Material, SoF Table 26]. Subsequently, the ACCENT II trial evaluated the efficacy of infliximab [5 mg/kg every 8 weeks] in a maintenance trial in 195 patients who had a response [defined as a reduction of 50% of draining fistulae in two visits at least 4 weeks apart] at week 14 after open-label induction treatment with infliximab. A complete response was maintained until week 54 in 19 of 99 placebo patients [19.2%] versus 33 of 96 infliximab patients [34.4%] [RR: 1.79; 95% CI: 1.10–2.92][142]. A meta-analysis of the existing data revealed that infliximab was found to be effective in inducing **fistula healing** [RR: 3.57; 95% CI:1.38–9.25] and in maintaining clinical **fistula healing** [RR: 1.79; 95% CI:1.10–2.92] with no significant risk of **serious AEs** as compared with placebo [RR: 1.31; 95% CI: 0.11–15.25] [Supplementary Figure 26]. A combined evaluation of both RCTs for **safety** revealed a risk of serious **AEs** of 18.9% [33/175 patients] in placebo groups versus 11.9% [24/201] in infliximab patients. These data from RCTs have been confirmed in several uncontrolled studies[143].

In clinical practice, infliximab is often used in combination with immunosuppressants, antibiotics, and surgical treatment[144-147]. Some retrospective data suggest that fistula healing is more likely in patients with higher infliximab trough levels, which suggests the need for personalized dosing in this setting[148,149].

Recommendation 3.2. ECCO CD Treatment GL [2019]

We suggest adalimumab may be used for induction and maintenance of remission in complex perianal fistulae in Crohn's disease (weak recommendation, very low-quality evidence).

Fistula healing in the subgroup of patients with enterocutaneous and/or perianal fistulae at baseline [n = 117] was a secondary endpoint of the CHARM double-blind, placebo-controlled, randomized trial[150]. A subsequent post-hoc analysis that focused specifically on the efficacy of adalimumab over time in this subgroup confirmed the superiority of adalimumab over placebo [RR: 2.57; 95% CI: 1.13–5.84] for **fistula healing** after 56 weeks[150] [Supplementary Material, SoF Table 27]. Data from CHARM combined with data from the open-label extension study ADHERE showed that there was no significant increase in **serious AEs** for patients treated with adalimumab [RR: 1.21; 95% CI: 0.43–3.38][102,151]. Evidence was also sought for maintenance of fistula healing beyond 56 weeks, resolution of perianal sepsis, stoma-free survival, and quality of life; however, data were insufficient. Although we strongly recommend infliximab as first-line biological therapy in complex perianal CD [Recommendation 3.1], adalimumab may have a role in patients with previous infliximab failure due to immunogenicity [either primary non-responders or secondary loss-of-responders]. The open-label CHOICE trial indeed demonstrated that complete fistula healing [mainly perianal fistula] could be achieved in 39% of patients [34/88] who initiated adalimumab after infliximab failure[152]. This finding has also been reported in a limited case series[153].

Recommendation 3.3. ECCO CD Treatment GL [2019]

In patients with Crohn's disease and complex perianal fistula there is insufficient evidence regarding the effect of adding immunomodulators to anti-TNF on fistula healing (weak recommendation, very low-quality evidence).

We identified a single study[75] [a pooled analysis of individual data from the intervention arms only of studies] that compared anti-TNF versus placebo. Only a pooled effect estimate was provided [i.e. OR of complete fistula closure in those on immunomodulators vs. those not on immunomodulators was 1.10; 95% CI: 0.68–1.78] without further information on numbers of patients by compared group. Therefore, event rates and absolute risk differences could not be calculated. Furthermore, a retrospective study revealed a hazard ratio of 2.58 [95% CI: 1.16–5.6] for fistula healing in favour of the intervention arm [combination infliximab and immunomodulator] in patients with CD naïve to immunosuppressive therapy[154]. There is thus insufficient evidence to support a decision for or against the use of immunomodulators in this context. Further research is necessary to reduce uncertainty and may be warranted considering the anticipated costs and side effects of combination therapy. In particular, we note the evidence in luminal CD, where addition of immunomodulators reduces immunogenicity of long-term anti-TNF therapy. We therefore recommend further research that should focus on the additional treatment effect of combination therapy and the impact on immunogenicity to anti-TNF agents.

Recommendation 3.4. ECCO CD Treatment GL [2019]

In patients with Crohn's disease and complex perianal fistula there is insufficient evidence to recommend the use of ustekinumab for fistula healing (weak recommendation, moderate-quality evidence).

No randomized trial has directly assessed the role of ustekinumab in fistula healing. A post-hoc analysis of 238 patients who entered the phase 2 CERTIFI and phase 3 UNITI 1/2 studies with fistulae at baseline has been reported[155] [Supplementary Material, SoF Table 28]. This study included only patients with perianal fistulae and did not differentiate between simple and complex fistulae. The analysis showed a measurable but statistically insignificant effect of ustekinumab for **induction of remission** [RR: 1.77, 95% CI:0.93–3.37] but no difference in comparison to placebo was found for **maintenance of remission**[156]. We also sought evidence for the effect of ustekinumab on longer-term **maintenance of fistula remission**, **serious AEs**, **resolution of perianal sepsis**, **stoma-free survival**, and **quality of life**; however, data were insufficient. Further research is therefore warranted to determine if ustekinumab is beneficial to patients with perianal fistulae.

Recommendation 3.5. ECCO CD Treatment GL [2019]

In patients with Crohn's disease and complex perianal fistula there is insufficient evidence to recommend the use of vedolizumab for fistula healing (weak recommendation, low-quality evidence).

A post-hoc analysis of 45 patients who entered the GEMINI 2 study with complex perianal fistulae at baseline demonstrated a trend in favour of vedolizumab compared to placebo for fistula healing [RR: 2.23; 95% CI: 0.57–8.72] although this result was not statistically significant[156,157] [Supplementary Material, SoF Table 29]. The interpretation of this study was limited by sparse data [only 13 patients met the endpoint across treatment arms] and specification of fistulae type [perianal in only 74% of patients]. Evidence was sought also for long-term maintenance of clinical **fistula healing, serious AEs, quality of life, resolution of perianal sepsis,** and **stoma-free survival**; however, data were insufficient. The only RCT [NCT02630966][158] that compared two different induction schedules of vedolizumab [300 mg at week 0, 2, 6, 10, and 14 vs. 300 mg at week 0, 2, 6, and 14] was prematurely stopped due to slow recruitment and therefore is

inconclusive. However, significant differences were observed between the two study groups. The efficacy of vedolizumab for fistula healing remains an important research gap.

Recommendation 3.6. ECCO CD Treatment GL [2019]

We suggest against using antibiotics alone for fistula closure in patients with Crohn's disease and complex perianal fistulae (weak recommendation, low-quality evidence).

Antibiotics are widely used in the treatment of perianal CD but most published studies are uncontrolled[144]. To our knowledge, there is only one RCT that compared placebo to antibiotics in perianal fistulae [Supplementary Material, SoF Table 30]. **Remission** at week 10 was observed in 1/8 [12.5%] placebo patients versus 3/17 [17.6%] patients treated with antibiotics [RR: 1.41; 95% CI: 0.17–11.54][159]. **Complete healing** was observed in 3/10 [30%] patients treated with ciprofloxacin and 0/8 patients treated with metronidazole. Uncontrolled data or data from studies on combination therapy with anti-TNF suggest that ciprofloxacin can improve the efficacy of anti-TNF in the short term with good **safety**. However, this combination does not impact longer-term healing rates[160,161]. Despite the lack of evidence to support their role as monotherapy in closing perianal fistulae, antibiotics remain indicated and recommended to treat and control perianal sepsis.

Recommendation 3.7. ECCO CD Treatment GL [2019]

We suggest against using thiopurine monotherapy (azathioprine, mercaptopurine) for fistula closure in patients with Crohn's disease and complex perianal fistulae (weak recommendation, very low-quality evidence).

The effect of AZA on **fistula healing** in complex perianal CD has been numerically reported in RCTs in 18 patients only[49,52,53,162]. A meta-analysis on this limited group of patients demonstrated that AZA is not superior to placebo for **fistula healing** [RR: 2.00; 95% CI: 0.67–5.93][96]. A fourth study[50] reported complete **fistula closure** in 9/29 [31%] fistulae during MP therapy, in contrast to 1/17 [6%] in placebo-treated fistulae [Supplementary Material, SoF Table 31]. Nevertheless, these data could not be incorporated in the pooled analysis, as data were reported as number of **fistulae closing** rather than number of patients who had complete **fistulae closing**. With the availability of effective anti-TNF agents, the group felt that it would be inappropriate to recommend any further randomized, placebo-controlled, double-blind trial studying the efficacy of AZA in complex perianal fistulae.

Key points for clinical practice

This section contains recommendations on the medical treatment of perianal disease. However, the management of complex perianal disease should be considered together with the concomitant treatment of luminal disease.

For the medical treatment of perianal fistulae, no evidence supports the use of monotherapy with antibiotics or thiopurines. The highest-quality evidence supports the use of infliximab as first choice. In patients refractory or intolerant to infliximab, there is low-quality evidence to support the use of adalimumab. The current evidence is too limited to support the use of ustekinumab and vedolizumab in clinical practice. However, ustekinumab or vedolizumab may be considered in patients where anti-TNFs are ineffective or contraindicated and there are no treatment options, especially when concomitant luminal disease is present. There is insufficient evidence on the use of combination therapy [specifically infliximab] combined with thiopurines. However, this can be considered when chosen as a therapy for concomitant luminal disease or for anti-immunogenicity purposes.

Although there is no randomized study that compared the combination of surgical treatment and infliximab with infliximab alone, joint management and approach by IBD clinicians and surgeons is considered the standard of care for treatment of complex perianal disease. This is important, since control of sepsis and prevention of perianal infections is necessary before starting any treatment that affects the immune system response. Any immunosuppressive treatment must be stopped in case of onset of septic complications in patients with IBD.

Conclusion

These recommendations summarize the current evidence on the medical management of patients with CD. Several research gaps have been identified during the revision and analysis of data, which should to be addressed by further research. Where evidence is lacking or is very weak and evidence-based recommendations cannot be given, ECCO provides alternative tools, such as Topical Reviews[21,93,138,163-165] or Position Papers[166]. While we state that Guidelines aim to guide the clinicians' decisions with the best evidence available, it is up to every clinician to adapt these Guidelines to local regulations and to the patient's individual characteristics and needs. ECCO will also aim to disseminate these guidelines by educational activities [i.e. educational platforms, ECCO Workshop, e-learning and e-Guide] and to support any initiative to integrate ECCO Guidelines into clinical practice; the ECCO e-Guide will primarily serve as a resource to examine how the Guideline recommendations can be implemented into daily clinical practice and patient care pathways[167]. These guidelines will be regularly updated according to the Guideline Committee outline for the update of Guidelines in the future, using the GRADE approach and considering the most recent evidence emerging from clinical research in the field.

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Authors' contribution

Joana Torres, Gionata Fiorino, Michel Adamina, Oded Zmora coordinated the project; Stefanos Bonovas, Theodore Lytras, and Marien Gonzalez-Lorenzo advised on GRADE methodology, trained the working group members, and performed the analysis of data; Glen Doherty, Torsten Kucharzik, Javier Gisbert, Timothy Raine, Antonino Spinelli, and Janindra Warusavitarne coordinated the working groups; all the Authors listed contributed to the identification of relevant data, data interpretation, drafted and discussed the final recommendations; all the Authors participated in the final Consensus; Gionata Fiorino, Joana Torres, Stefanos Bonovas, Glen Doherty, Torsten Kucharzik, Javier Gisbert, and Tim Raine drafted this manuscript; all Authors, the ECCO Guideline Committee [GuiCom], and the ECCO Governing Board approved the final version of the manuscript.

Conflict of interests

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI disclosures are not only stored at the ECCO Office and the editorial office of JCC but are also open to public scrutiny on the ECCO Website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of the Authors.

References

1. Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017;**389**:1741-55.

2. Keyashian K, Dehghan M, Sceats L, *et al.* Comparative Incidence of Inflammatory Bowel Disease in Different Age Groups in the United States. *Inflamm Bowel Dis* 2019.

3. Jones G-R, Lyons M, Plevris N, *et al.* IBD prevalence in Lothian, Scotland, derived by capture–recapture methodology. *Gut* 2019:gutjnl-2019-318936.

4. Cosnes J, Cattan S, Blain A, *et al.* Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;**8**:244-50.

5. Kruis W, Katalinic A, Klugmann T, *et al.* Predictive factors for an uncomplicated long-term course of Crohn's disease: a retrospective analysis. *J Crohns Colitis* 2013;**7**:e263-70.

6. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut* 2017;**66**:2179-87.

7. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *The American journal of gastroenterology* 2010;**105**:289-97.

8. Gomollón F, Dignass A, Annese V, *et al.* 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *Journal of Crohn's and Colitis* 2017;**11**:3-25.

9. Atkins D, Best D, Briss PA, *et al.* Grading quality of evidence and strength of recommendations. *BMJ (Clinical research ed)* 2004;**328**:1490-.

10. Gionchetti P, Dignass A, Danese S, *et al.* 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 2: Surgical management and special situations. *Journal of Crohn's and Colitis* 2017;**11**:135-49.

11. Nahon S, Lahmek P, Lesgourgues B, *et al.* Diagnostic delay in a French cohort of Crohn's disease patients. *J Crohns Colitis* 2014;**8**:964-9.

12. Schoepfer AM, Dehlavi MA, Fournier N, *et al.* Diagnostic delay in Crohn's disease is associated with a complicated disease course and increased operation rate. *The American journal of gastroenterology* 2013;**108**:1744-53; quiz 54.

13. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV, Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010;**139**:1147-55.

14. Vavricka SR, Spigaglia SM, Rogler G, *et al.* Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:409-505.

15. Khanna R, Bressler B, Levesque B, *et al.* Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet (london, england)* 2015;**386**:1825-34.

16. Colombel JJ-F, Panaccione R, Bossuyt P, *et al.* Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet (london, england)* 2018;**390**:2779-89.

17. Maaser C, Sturm A, Vavricka SR, *et al.* ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;**13**:144-64.

18. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *The American journal of gastroenterology* 2015;**110**:1324-38.

19. Annese V, Beaugerie L, Egan L, *et al.* European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. *J Crohns Colitis* 2015;**9**:945-65.

20. Rahier JF, Magro F, Abreu C, *et al.* Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014;**8**:443-68.

21. Sigall-Boneh R, Levine A, Lomer M, *et al.* Research Gaps in Diet and Nutrition in Inflammatory Bowel Disease. A Topical Review by D-ECCO Working Group [Dietitians of ECCO]. *J Crohns Colitis* 2017;**11**:1407-19.

22. Harbord M, Annese V, Vavricka SR, *et al.* The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. *J Crohns Colitis* 2016;**10**:239-54.

23. Adamina M, Gerasimidis K, Sigall-Boneh R, *et al.* Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis* 2019.

24. Ford AC, Kane SV, Khan KJ, *et al.* Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *The American journal of gastroenterology* 2011;**106**:617-29.

25. Rasmussen SN, Lauritsen K, Tage-Jensen U, *et al.* 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. *Scand J Gastroenterol* 1987;**22**:877-83.

26. Singleton JW, Hanauer SB, Gitnick GL, *et al.* Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993;**104**:1293-301.

27. Tremaine WJ, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994;**19**:278-82.

28. No Authors listed PEACE study: a study with pentasa in patients with active crohn's disease. 2012. Last Update on March 16, 2012, Accessed on Sep 16, , 2019, Available on https://clinicaltrials.gov/ct2/show/NCT00862121

29. Malchow H, Ewe K, Brandes JW, *et al.* European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;**86**:249-66.

30. Summers RW, Switz DM, Sessions JT, Jr., *et al.* National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;**77**:847-69.

31. Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2016;**7**:CD008870.

32. Coward S, Kuenzig ME, Hazlewood G, *et al.* Comparative Effectiveness of Mesalamine, Sulfasalazine, Corticosteroids, and Budesonide for the Induction of Remission in Crohn's Disease: A Bayesian Network Meta-analysis: Republished. *Inflamm Bowel Dis* 2017;**23**:E26-E37.

33. Moja L, Danese S, Fiorino G, Del Giovane C, Bonovas S. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine (mesalamine) for Crohn's disease. *Aliment Pharmacol Ther* 2015;**41**:1055-65.

34. Hanauer SB, Stromberg U. Oral Pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004;**2**:379-88.

35. Rezaie A, Kuenzig ME, Benchimol EI, *et al.* Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd, 2015.

36. Greenberg GR, Feagan BG, Martin F, *et al.* Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *N Engl J Med* 1994;**331**:836-41.

37. Tremaine WJ, Hanauer SB, Katz S, *et al.* Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. *The American journal of gastroenterology* 2002;**97**:1748-54.

38. Suzuki Y, Motoya S, Takazoe M, *et al.* Efficacy and tolerability of oral budesonide in Japanese patients with active Crohn's disease: a multicentre, double-blind, randomized, parallel-group Phase II study. *J Crohns Colitis* 2013;**7**:239-47.

39. Thomsen OO, Cortot A, Jewell D, *et al.* A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 1998;**339**:370-4.

40. Tromm A, Bunganic I, Tomsova E, *et al.* Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. *Gastroenterology* 2011;**140**:425-34 e1; quiz e13-4.

41. Yokoyama T, Ohta A, Motoya S, *et al.* Efficacy and Safety of Oral Budesonide in Patients with Active Crohn's Disease in Japan: A Multicenter, Double-Blind, Randomized, Parallel-Group Phase 3 Study. *Inflamm Intest Dis* 2018;**2**:154-62.

42. Khan KJ, Ullman TA, Ford AC, *et al.* Antibiotic therapy in inflammatory bowel disease: A systematic review and meta-analysis. *American Journal of Gastroenterology* 2011;**106**:661-73.

43. Lichtenstein GR, Loftus EV, Isaacs KL, *et al.* ACG Clinical Guideline: Management of Crohn's Disease in Adults. *The American journal of gastroenterology* 2018;**113**:481-517.

44. Selby W, Pavli P, Crotty B, *et al.* Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology* 2007;**132**:2313-9.

45. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008:CD006792.

46. Singleton JW, Law DH, Kelley ML, Jr., Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. *Gastroenterology* 1979;**77**:870-82.

47. Candy S, Wright J, Gerber M, *et al.* A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995;**37**:674-8.

48. Ewe K, Press AG, Singe CC, *et al.* Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. *Gastroenterology* 1993;**105**:367-72.

49. Klein M, Binder HJ, Mitchell M, Aaronson R, Spiro H. Treatment of Crohn's disease with azathioprine: a controlled evaluation. *Gastroenterology* 1974;**66**:916-22.

50. Present DH, Korelitz BI, Wisch N, *et al.* Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980;**302**:981-7.

51. Reinisch W, Panes J, Lemann M, *et al.* A multicenter, randomized, double-blind trial of everolimus versus azathioprine and placebo to maintain steroid-induced remission in patients with moderate-to-severe active Crohn's disease. *The American journal of gastroenterology* 2008;**103**:2284-92.

52. Rhodes J, Bainton D, Beck P, Campbell H. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;**2**:1273-6.

53. Willoughby JM, Beckett J, Kumar PJ, Dawson AM. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;**2**:944-7.

54. Oren R, Moshkowitz M, Odes S, *et al.* Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *The American journal of gastroenterology* 1997;**92**:2203-9.

55. Feagan BG, Rochon J, Fedorak RN, *et al.* Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995;**332**:292-7.

56. Oren R, Arber N, Odes S, *et al.* Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996;**110**:1416-21.

57. Oren R, Moshkowitz M, Odes S, *et al.* Erratum: methotrexate in chronic active crohn's disease: a double-blind, randomized, israeli multicenter trial (American Journal of Gastroenterology (1997) 92 (2203-2209)). *American journal of gastroenterology* 2015;**110**:608.

58. Oren R, Moshkowitz M, Odes S, *et al.* Corrigendum: methotrexate in chronic active Crohn's disease: a double-blind, randomized, israeli multicenter trial. *The American journal of gastroenterology* 2015;**110**:608.

59. Mate-Jimenez J, Hermida C, Cantero-Perona J, *et al.* 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. *European journal of gastroenterology & hepatology* 2000;**12**:1227-33.

60. Ardizzone S, Bollani S, Manzionna G, *et al.* Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Digestive and liver disease* 2003;**35**:619-27.

61. van der Woude CJ, Ardizzone S, Bengtson MB, *et al.* The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease. *Journal of Crohn's and Colitis* 2015;**9**:107-24.

62. Stidham RW, Lee TCH, Higgins PDR, *et al.* Systematic review with network meta-analysis: The efficacy of anti-TNF agents for the treatment of Crohn's disease. *Alimentary Pharmacology and Therapeutics* 2014;**39**:1349-62.

63. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther* 2017;**45**:1291-302.

64. Ford AC, Sandborn WJ, Khan KJ, *et al.* Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *The American journal of gastroenterology* 2011;**106**:644-59, quiz 60.

65. Rutgeerts P, Diamond RH, Bala M, *et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006;**63**:433-42; quiz 64.

66. Rutgeerts P, Van Assche G, Sandborn WJ, *et al.* Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012;**142**:1102-11.e2.

67. Hazlewood GS, Rezaie A, Borman M, *et al.* Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology* 2015;**148**:344-5.

68. Colombel JF, Reinisch W, Mantzaris GJ, *et al.* Randomised clinical trial: deep remission in biologic and immunomodulator naive patients with Crohn's disease - a SONIC post hoc analysis. *Alimentary pharmacology & therapeutics* 2015;**41**:734-46.

69. Colombel JF, Rutgeerts PJ, Sandborn WJ, *et al.* Adalimumab induces deep remission in patients with Crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2014;**12**:414-22 e5.

70. Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *The New England journal of medicine* 2010;**362**:1383-95.

71. Colombel JF, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**:52-65.

72. Schreiber S, Reinisch W, Colombel JF, *et al.* Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *Journal of Crohn's & colitis* 2013;**7**:213-21.

73. Matsumoto T, Motoya S, Watanabe K, *et al.* Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: A Prospective, Randomized Trial. *J Crohns Colitis* 2016;**10**:1259-66.

74. Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *New England journal of medicine* 2010;**362**:1383-95.

75. Jones JL, Kaplan GG, Peyrin-Biroulet L, *et al.* Effects of Concomitant Immunomodulator Therapy on Efficacy and Safety of Anti-Tumor Necrosis Factor Therapy for Crohn's Disease: A Meta-analysis of Placebo-controlled Trials. *Clin Gastroenterol Hepatol* 2015;**13**:2233-40 e1-2; quiz e177-8.

76. European Medicine Agency Stelara - Ustekinumab. 2009. Last Update on Sep 2019, Accessed on Sep 16, 2019, Available on https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf

77. Sandborn W, Gasink C, Gao L, *et al.* Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *New England journal of medicine* 2012;**367**:1519-28.

78. MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2016;**11**:CD007572.

79. Sandborn WJ, Feagan BG, Fedorak RN, *et al.* A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008;**135**:1130-41.

80. Feagan BG, Sandborn WJ, Gasink C, *et al.* Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *New England journal of medicine* 2016;**375**:1946-60.

81. Rutgeerts P, Gasink C, Chan D, *et al.* Efficacy of Ustekinumab in Inducing Endoscopic Healing in Patients with Crohn's Disease. *Gastroenterology* 2018;**155**:1045-58.

82. Hanauer SB, Sandborn WJ, Feagan BG, *et al.* IM-UNITI: 3 Year Efficacy, Safety, and Immunogenicity of Ustekinumab Treatment of Crohn's Disease. *J Crohns Colitis* 2019.

83. Sandborn WJ, Feagan BG, Rutgeerts P, *et al.* Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;**369**:711-21.

84. European Medicine Agency Entyvio - Summary of Product Characteristics. 2014. Last Update on Apr 2019, Accessed on Sep 16, 2019, Available on https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf

85. Feagan BG, Greenberg GR, Wild G, *et al.* Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. *Clin Gastroenterol Hepatol* 2008;**6**:1370-7.

86. Sands B, Feagan B, Rutgeerts P, *et al.* Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology, 2014: 618-27.e3.

87. Kawalec P, Mocko P. An indirect comparison of ustekinumab and vedolizumab in the therapy of TNF-failure Crohn's disease patients. *J Comp Eff Res* 2018;**7**:101-11.

88. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2003:Cd000301.

89. Kalman RS, Hartshorn K, Farraye FA. Does a personal or family history of malignancy preclude the use of immunomodulators and biologics in IBD. *Inflamm Bowel Dis* 2015;**21**:428-35.

90. Kennedy NA, Heap GA, Green HD, *et al.* Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019;**4**:341-53.

91. Kirchgesner J, Lemaitre M, Carrat F, *et al.* Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. *Gastroenterology* 2018;**155**:337-46 e10.

92. Lemaitre M, Kirchgesner J, Rudnichi A, *et al.* Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. *JAMA* 2017;**318**:1679-86.

93. Sturm A, Maaser C, Mendall M, *et al.* European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly. *J Crohns Colitis* 2017;**11**:263-73.

94. Beaugerie L. Lymphoma: the bete noire of the long-term use of thiopurines in adult and elderly patients with inflammatory bowel disease. *Gastroenterology* 2013;**145**:927-30.

95. Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2016;**9**:Cd003715.

96. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015:Cd000067.

97. Lemann M, Mary JY, Colombel JF, *et al.* A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005;**128**:1812-8.

98. O'Donoghue DP, Dawson AM, Powell-Tuck J, Bown RL, Lennard-Jones JE. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. *Lancet* 1978;**2**:955-7.

99. Panés J, López-Sanromán A, Bermejo F, *et al.* Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. *Gastroenterology* 2013;**145**:766-74.e1.

100. Rosenberg JL, Levin B, Wall AJ, Kirsner JB. A controlled trial of azathioprine in Crohn's disease. *Am J Dig Dis* 1975;**20**:721-6.

101. Cosnes J, Bourrier A, Laharie D, *et al.* Early administration of azathioprine vs conventional management of Crohn's disease: a randomized controlled trial. *Gastroenterology* 2013;**145**:755-8.

102. Colombel J, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial. *Gastroenterology* 2007;**132**:52-65.

103. Hanauer S, Feagan B, Lichtenstein G, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet (london, england)* 2002;**359**:1541-9.

104. Sandborn WJ, Feagan BG, Honiball PJ, *et al.* Certolizumab pegol for the treatment of Crohn's disease. *New England journal of medicine* 2007;**357**:228-38.

105. Sandborn WJ, Hanauer SB, Rutgeerts P, *et al.* Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial. *Gut* 2007;**56**:1232-9.

106. Schreiber S, Khaliq-Kareemi M, Lawrance IC, *et al.* Maintenance therapy with certolizumab pegol for Crohn's disease. *New England journal of medicine* 2007;**357**:239-50.

107. Singh JA, Wells GA, Christensen R, *et al.* Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011:CD008794.

108. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther* 2018;**48**:394-409.

109. Vande Casteele N, Ferrante M, Van Assche G, *et al.* Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015;**148**:1320-9 e3.

110. D'Haens G, Vermeire S, Lambrecht G, *et al.* Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. *Gastroenterology* 2018;**154**:1343-51 e1.

111. Steenholdt C, Brynskov J, Thomsen OO, *et al.* Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut* 2014;**63**:919-27.

112. Feuerstein JD, Nguyen GC, Kupfer SS, *et al.* American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology* 2017;**153**:827-34.

113. Mitrev N, Leong RW. Therapeutic drug monitoring of anti-tumour necrosis factor-α agents in inflammatory bowel disease. *Expert Opinion on Drug Safety* 2017;**16**:303-17.

114. Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. Therapeutic Drug Monitoring to Guide Infliximab Dose Adjustment is Associated with Better Endoscopic Outcomes than Clinical Decision Making Alone in Active Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2017;**23**:1202-9.

115. Guidi L, Pugliese D, Panici Tonucci T, *et al.* Therapeutic drug monitoring is more cost-effective than a clinically-based approach in the management of loss of response to infliximab in inflammatory bowel disease: an observational multi-centre study. *J Crohns Colitis* 2018.

116. Ricciuto A, Dhaliwal J, Walters TD, Griffiths AM, Church PC. Clinical Outcomes With Therapeutic Drug Monitoring in Inflammatory Bowel Disease: A Systematic Review With Meta-Analysis. *J Crohns Colitis* 2018;**12**:1302-15.

117. O'Donoghue DP, Dawson AM, Powell-Tuck J, Bown RL, Lennard-Jones JE. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. *Lancet* 1978;**2**:955-7.

118. Vilien M, Dahlerup JF, Munck LK, *et al.* Randomized controlled azathioprine withdrawal after more than two years treatment in Crohn's disease: increased relapse rate the following year. *Alimentary pharmacology & therapeutics* 2004;**19**:1147-52.

119. Wenzl HH, Primas C, Novacek G, *et al.* Withdrawal of long-term maintenance treatment with azathioprine tends to increase relapse risk in patients with Crohn's disease. *Digestive diseases and sciences* 2015;**60**:1414-23.

120. Boyapati RK, Torres J, Palmela C, *et al.* Withdrawal of immunosuppressant or biologic therapy for patients with quiescent Crohn's disease. *Cochrane Database Syst Rev* 2018;**5**:CD012540.

121. Roblin X, Boschetti G, Williet N, *et al.* Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. *Aliment Pharmacol Ther* 2017;**46**:142-9.

122. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, *et al.* Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology* 2008;**134**:1861-8.

123. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;**7**:874-81.

124. Chalhoub JM, Rimmani HH, Gumaste VV, Sharara AI. Systematic Review and Meta-analysis: Adalimumab Monotherapy Versus Combination Therapy with Immunomodulators for Induction and Maintenance of Remission and Response in Patients with Crohn's Disease. *Inflammatory bowel diseases* 2017;**23**:1316-27.

125. Kamm MA, Hanauer SB, Rutgeerts P, *et al.* Results from an open-label extension of CHARM: Steroid-free remission in patients with Crohn's disease who received Adalimumab therapy for at least 3 years. *Gastroenterology* 2009;**136**:A653.

126. Torres J, Boyapati RK, Kennedy NA, *et al.* Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients With Inflammatory Bowel Disease. *Gastroenterology* 2015;**149**:1716-30.

127. Gisbert JP, Marin AC, Chaparro M. The Risk of Relapse after Anti-TNF Discontinuation in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. *The American journal of gastroenterology* 2016;**111**:632-47.

128. Kennedy NA, Warner B, Johnston EL, *et al.* Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. *Aliment Pharmacol Ther* 2016.

129. Casanova MJ, Chaparro M, Garcia-Sanchez V, *et al.* Evolution After Anti-TNF Discontinuation in Patients With Inflammatory Bowel Disease: A Multicenter Long-Term Follow-Up Study. *The American journal of gastroenterology* 2017;**112**:120-31.

130. Helwig U, Lutter F, Koppka N, Schreiber S. Proposal for an anti-tumour necrosis factor-exit strategy based on trough serum level. *Journal of Crohn's and Colitis* 2016;**10**:S252-S3.

131. Papamichael K, Rivals O, Billiet T, *et al.* Long-term outcome of IBD patients with primary non-response to anti-TNF therapy. *Journal of Crohn's and Colitis* 2015;**9**:S864.

132. Hlavaty T, Krajcovicova A, Letkovsky J, *et al.* Relapse rates of inflammatory bowel disease patients in deep and clinical remission after discontinuing anti-tumor necrosis factor alpha therapy. *Bratisl Lek Listy* 2016;**117**:205-11.

133. Bortlik M, Duricova D, Machkova N, *et al.* Discontinuation of anti-tumor necrosis factor therapy in inflammatory bowel disease patients: a prospective observation. *Scand J Gastroenterol* 2016;**51**:196-202.

134. Molander P, Farkkila M, Kemppainen H, *et al.* Long-term outcome of inflammatory bowel disease patients with deep remission after discontinuation of TNFalpha-blocking agents. *Scand J Gastroenterol* 2017;**52**:284-90.

135. Reenaers C, Mary JY, Nachury M, *et al.* Outcomes 7 Years After Infliximab Withdrawal for Patients With Crohn's Disease in Sustained Remission. *Clin Gastroenterol Hepatol* 2018;**16**:234-43.e2.

136. Hu H, Xiang C, Qiu C, *et al.* Discontinuation of Scheduled Infliximab in Crohn's Patients With Clinical Remission: A Retrospective Single-Center Study. *Gastroenterology Res* 2017;**10**:92-9.

137. Ampuero J, Rojas-Feria M, Castro-Fernandez M, *et al.* Remission maintained by monotherapy after biological + immunosuppressive combination for Crohn's disease in clinical practice. *J Gastroenterol Hepatol* 2016;**31**:112-8.

138. Doherty G, Katsanos KH, Burisch J, *et al.* European Crohn's and Colitis Organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *Journal of Crohn's and Colitis* 2018;**12**:17-31.

139. Beaugerie L, Brousse N, Bouvier AM, *et al.* Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;**374**:1617-25.

140. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, *et al.* Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011;**141**:1621-28 e1-5.

141. Present DH, Rutgeerts P, Targan S, *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *New England journal of medicine* 1999;**340**:1398-405.

142. Sands BE, Anderson FH, Bernstein CN, *et al.* Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. *New England journal of medicine* 2004;**350**:876-85.

143. Bermejo F, Guerra I, Algaba A, Lopez-Sanroman A. Pharmacological Approach to the Management of Crohn's Disease Patients with Perianal Disease. *Drugs* 2018;**78**:1-18.

144. Panes J, Rimola J. Perianal fistulizing Crohn's disease: pathogenesis, diagnosis and therapy. *Nat Rev Gastroenterol Hepatol* 2017;**14**:652-64.

145. Kotze PG, Shen B, Lightner A, *et al.* Modern management of perianal fistulas in Crohn's disease: future directions. *Gut* 2018;**67**:1181-94.

146. Steinhart AH, Panaccione R, Targownik L, *et al.* Clinical Practice Guideline for the Medical Management of Perianal Fistulizing Crohn's Disease: The Toronto Consensus. *Inflamm Bowel Dis* 2019;**25**:1-13.

147. Regueiro M, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. *Inflamm Bowel Dis* 2003;**9**:98-103.

148. Yarur AJ, Kanagala V, Stein DJ, *et al.* Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther* 2017;**45**:933-40.

149. Davidov Y, Ungar B, Bar-Yoseph H, *et al.* Association of Induction Infliximab Levels With Clinical Response in Perianal Crohn's Disease. *J Crohns Colitis* 2017;**11**:549-55.

150. Colombel JF, Schwartz DA, Sandborn WJ, *et al.* Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut* 2009;**58**:940-8.

151. Panaccione R, Colombel JF, Sandborn WJ, *et al.* Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. *Aliment Pharmacol Ther* 2013;**38**:1236-47.

152. Lichtiger S, Binion DG, Wolf DC, *et al.* The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. *Alimentary pharmacology & therapeutics* 2010;**32**:1228-39.

153. Echarri A, Castro J, Barreiro M, *et al.* Evaluation of adalimumab therapy in multidisciplinary strategy for perianal Crohn's disease patients with infliximab failure. *J Crohns Colitis* 2010;**4**:654-60.

154. Bouguen G, Siproudhis L, Gizard E, *et al.* Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol* 2013;**11**:974-5.

155. Sands BE, Gasink C, Jacobstein D, *et al.* Fistula Healing in Pivotal Studies of Ustekinumab in Crohn's Disease. *Gastroenterology* 2017;**152**:S185.

156. Lee MJ, Parker CE, Taylor SR, *et al.* Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018;**16**:1879-92.

157. Feagan BG, Schwartz D, Danese S, *et al.* Efficacy of Vedolizumab in Fistulising Crohn's Disease: Exploratory Analyses of Data from GEMINI 2. *J Crohns Colitis* 2018;**12**:621-6.

158. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT00287391 SdagrdG Identifier NCT02630966, Vedolizumab IV 300 mg in the Treatment of Fistulizing Crohn's Disease (ENTERPRISE) 2015. Last Update on November 19, 2018 Accessed on April 1, 2019, Available on https://clinicaltrials.gov/ct2/show/study/NCT02630966

159. Thia KT, Mahadevan U, Feagan BG, *et al.* Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009;**15**:17-24.

160. Khan KJ, Ullman TA, Ford AC, *et al.* Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011;**106**:661-73.

161. Dewint P, Hansen BE, Verhey E, *et al.* Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). *Gut* 2014;**63**:292-9.

162. Willoughby JM, Kumar P, Beckett J, Dawson AM. A double-blind trial of azathioprine in Crohn's disease. *Gut* 1971;**12**:864.

163. Maaser C, Langholz E, Gordon H, *et al.* European Crohn's and Colitis Organisation Topical Review on Environmental Factors in IBD. *J Crohns Colitis* 2017;**11**:905-20.

164. Rieder F, Latella G, Magro F, *et al.* European Crohn's and Colitis Organisation Topical Review on Prediction, Diagnosis and Management of Fibrostenosing Crohn's Disease. *J Crohns Colitis* 2016;**10**:873-85.

165. van Rheenen PF, Aloi M, Biron IA, *et al.* European Crohn's and Colitis Organisation Topical Review on Transitional Care in Inflammatory Bowel Disease. *J Crohns Colitis* 2017;**11**:1032-8.

166. Danese S, Fiorino G, Raine T, *et al.* ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease-An Update. *J Crohns Colitis* 2017;**11**:26-34.

167. European Crohn's Colitis Organisation ECCO e-Guide. 2013. Last Update on Accessed on Oct 2, 2019, Available on https://www.ecco-ibd.eu/publications/ecco-guidelines-science/ecco-e-guide.html