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ECCO Guideline/Consensus Paper

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Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management

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Section 11. Medical Management of Active Ulcerative Colitis

11.1. General

The treatment strategy for ulcerative colitis [UC] is mainly based on the severity, distribution [proctitis, left-sided, extensive][1] and pattern of disease. The latter includes relapse frequency, disease course, response to previous medications, side effects of medication, and extra-intestinal manifestations. Age at onset, and disease duration are also important factors. It is important to distinguish patients with severe UC necessitating hospital admission from those with mild or moderately active disease who can be managed as outpatients. The best validated and most widely used index for identifying severe UC remains that of Truelove and Witts.[2] Patients with bloody stool frequency ≥ 6/day and a tachycardia [> 90 min^{-1}], *or* temperature > 37.8°C, *or* anaemia [haemoglobin < 10.5 g/dl], *or* an elevated erythrocyte sedimentation rate [ESR] [> 30 mm/h] have severe UC. Only one additional criterion in addition to the bloody stool frequency ≥ 6/day is needed to define a severe attack.[3,4] In practice, a C-reactive protein [CRP] of 30 mg/l can be substituted for the ESR.

11.2. Treatment according to site of disease and disease activity

11.2.1. Proctitis

ECCO statement 11A

A mesalamine 1-g suppository once daily is the preferred initial treatment for mild or moderately active proctitis [EL1]. Mesalamine foam or enemas are an alternative [EL1], but suppositories deliver the drug more effectively to the rectum and are better tolerated [EL3]. Topical mesalamine is more effective than topical steroids [EL1]. Combining topical mesalamine with oral mesalamine or topical steroids is more effective [EL2]

ECCO statement 11B

Refractory proctitis may require treatment with systemic steroids, immunosuppressants, and/or biologics [EL4]

Topical mesalamine [5-aminosalicylic acid or 5-ASA] is the first-line therapy for proctitis. A Cochrane systematic review of 38 clinical trials of treatment of proctitis and left-sided colitis confirmed its superiority over placebo for inducing symptomatic, endoscopic, histological response and remission.[5] The pooled odds ratio [OR] was: 8.3 for symptomatic remission (8 trials, 95% confidence interval [CI] 4.28–16.12; $p < 0.00001$); 5.3 for endoscopic remission [7 trials, 95% CI 3.15–8.92; $p < 0.00001$]; and 6.3 for histological remission [5 trials, 95% CI 2.74–14.40; $p < 0.0001$]. Suppositories are more appropriate than enemas in proctitis as they better target the site of inflammation and are more acceptable for patients.[6] There is no dose response for topical therapy above a dose of 1 g 5-ASA daily.[5,7] Once-daily topical therapy is as effective as divided doses.[8,9]

A meta-analysis found no difference between oral and topical 5-ASA for induction of remission (risk ratio [RR] for no remission with topical 5-ASA: 0.82, 95% CI 0.52–1.28) or time to remission [24.8 vs 25.5 days, respectively], but the trials included in this meta-analysis enrolled patients with UC of any extent, not specifically proctitis.[10] In the single trial that included only patients with proctitis, rectal 5-ASA was more effective than oral 5-ASA alone.[11] However, if oral 5-ASA is used alone, 3.6 g of a pH-dependent release preparation appears to be more effective than lower doses or placebo.[12] Moreover in patients with proctosigmoiditis, 5-ASA granules rather than tablets are more likely to obtain clinical [78% vs 55%, $p < 0.001$] and endoscopic [67% vs 43%, $p < 0.001$] remission.[13]

The combination of oral and topical 5-ASA is more effective than either alone in patients with disease extending < 50 cm from the anal verge,[14] although there is no trial of combination therapy for proctitis alone. Combining topical 5-ASA and topical steroids also helps: beclomethasone dipropionate [3 mg] and 5-ASA [2 g] enemas produced significantly better clinical, endoscopic, and histological improvement than either agent alone.[15]

Two meta-analyses have shown that topical 5-ASA is more effective than topical steroids, whether assessing symptomatic, endoscopic, or histological remission.[16] Consequently topical steroids should be prescribed to patients who have an inadequate response, or who are intolerant to topical 5-ASA.[17] A randomised trial has shown that 2 g budesonide rectal foam alone is more successful than placebo in inducing remission at Week 6 in patients with mild to moderate proctosigmoiditis [41.2% vs 24%, $p < 0.0001$].[18] This drug has not been compared with topical 5-ASA.

Compliance and endoscopic activity should be confirmed in those with failure to improve with oral plus topical 5-ASA and/or topical steroids. Refractory proctitis may require treatment with systemic steroids, immunomodulators [IMs], or biologics. The management of refractory proctitis is discussed in section 11.2.7.

11.2.2. Left-sided ulcerative colitis

ECCO statement 11C

Mild to moderately active left-sided ulcerative colitis should initially be treated with an aminosalicylate enema ≥ 1 g/day [EL1] combined with oral mesalamine ≥ 2.4 g/day [EL1], which is more effective than oral or topical aminosalicylates, or topical steroids alone [EL1]. Topical mesalamine is more effective than topical steroids [EL1]. Once-daily dosing with mesalamine is as effective as divided doses [EL1]

ECCO statement 11D

Systemic corticosteroids are appropriate in patients with moderate to severe activity and in those with mild activity who do not respond to mesalamine [EL1]. Oral beclomethasone dipropionate 5 mg/day has similar efficacy and safety profile as oral prednisone in patients with mild to moderately active ulcerative colitis [EL2]. Budesonide MMX 9 mg/day can be considered in patients with mild to moderate disease who are intolerant or refractory to aminosalicylates [EL2]. Severe left-sided colitis is an indication for hospital admission [EL1]

Combined oral and topical 5-ASA is the first-line therapy for mild to moderately active left-sided colitis, with an RR of failure to achieve remission of 0.65 [95% CI = 0.47–0.91] and shorter time to remission [11.9 vs 25.5 days; $p = 0.002$], as compared with oral 5-ASA alone.[10] However, either oral or topical 5-ASA alone is more effective than placebo.[5,10,19] Topical therapy achieves higher rectal mucosal 5-ASA concentrations than oral therapy.[20] No statistical differences were found between foam and liquid enemas regarding induction of remission[21] or endoscopic healing,[7] so either are appropriate treatments for left-sided UC. Low-volume enemas are not inferior to high-volume enemas and may be better tolerated.[22] Although several meta-analyses have confirmed the superiority of rectal 5-ASA over rectal corticosteroids,[5,16] a meta-analysis of three trials has suggested that rectal beclomethasone diproprionate is equivalent to rectal 5-ASA.[2]. Evidence exists that 2 g budesonide rectal foam alone is able to induce remission at Week 6 for mild to moderate left-sided UC.[18] Combination trials with oral and/or rectal 5-ASA and 2 g budesonide foam or enemas are needed.

Oral 5-ASA is no more effective than oral sulphasalazine [RR for failure to achieve remission 0.90, 95% CI 0.77–1.04] but is better tolerated [RR for an adverse event 0.48, 95% CI 0.36–0.63].[24] There is no difference in efficacy or adherence between once-daily and divided doses of 5-ASA[25,26] nor between the various 5-ASA formulations.[24,27] It was acknowledged, however, that once-daily dosing is likely to improve compliance outside the clinical trial environment; ≥ 2 g/day oral 5-ASA induces remission more effectively than lower doses [RR for failure to achieve remission at Weeks 4–8 of 0.91, 95% CI 0.85–0.98].[19] Patients with moderate disease may benefit from the higher dose of 4.8 g/day.[24]

The threshold for the introduction of oral steroids in patients with mild to moderate left-sided UC depends upon the response to and tolerance of 5-ASA, patient's preference and the physician's practice. In the ASCEND II trial, the median time to cessation of rectal bleeding was 9 days in patients receiving 4.8 g 5-ASA/day and 16 days in those receiving 2.4 g/day[28]; it was 7 days for 4.8 g/day MMX 5-ASA, although 37–45 days of therapy were required before sustained complete remission was achieved.[29,30] Therefore, if a patient's symptoms deteriorate, rectal bleeding persists beyond 10–14 days, or sustained relief from all symptoms has not been achieved after 40 days of appropriate 5-ASA therapy, additional therapy with oral systemic steroids should be started. However, open-label data suggested that a significant proportion of patients who have not responded to 8 weeks' oral 5-ASA may enter clinical remission after a further 8 weeks of 4.8 g MMX 5-ASA, irrespective of the initial dosing regimen.[31]

Oral beclomethasone dipropionate is non-inferior to but not better tolerated than prednisone after 4 weeks' treatment.[32] Oral

non-MMX budesonide does not appear to be efficient in the treatment of UC.[33] Two phase 3 randomised controlled trials [RCTs] [Core I and Core II][34,35] have compared oral budesonide MMX 9 mg/day with placebo in patients with mild to moderate left-sided and extensive UC. The 8-week combined clinical and endoscopic remission rates were 20.3% vs 3.2% [p = 0.0018]; and endoscopic healing rates were 27.6% vs 17.1% [p = 0.009], for budesonide MMX and placebo respectively.[36] In the Core I trial, budesonide MMX was also compared with oral Asacol at a dose of 2.4 g/day and no difference was found.[34] In the Core II trial, budesonide MMX was also compared with non-MMX budesonide and no difference was found,[35] although the study was not adequately powered to do so. Subgroup analysis of both trials demonstrated that the benefit of budesonide MMX is confined to left-sided disease and not extensive colitis.[36] Another randomised trial compared budesonide MMX with oral 5-ASA granules 3 g/day in 343 patients with mild to moderately active UC, most of whom had proctosigmoiditis or left-sided colitis. Mesalamine was numerically but not statistically superior to budesonide MMX [8-week clinical remission rate of 54.8 % vs 39.5%; p = 0.052].[37] A randomised trial has compared oral budesonide MMX with placebo in patients with mild to moderately active UC inadequately controlled with oral 5-ASA. Budesonide MMX 9 mg/day induced clinical, endoscopic and histological remission at Week 8 more frequently than placebo,[38] providing evidence for an alternative therapy to escalating to conventional steroids. However, there has been no head-to-head comparative trial between budesonide MMX and conventional steroids.[39]

11.2.3. Extensive ulcerative colitis

ECCO statement 11E

Mild to moderately active extensive ulcerative colitis should initially be treated with an aminosalicylate enema 1 g/day [EL1] combined with oral mesalamine ≥ 2.4 g/day [EL1]. Once-daily dosing with mesalamine is as effective as divided doses [EL1]. Systemic corticosteroids are appropriate in patients with moderate to severe activity and in those with mild activity who do not respond to mesalamine [EL1]. Severe extensive colitis is an indication for hospital admission for intensive treatment [EL1]

As the majority of clinical trials in mild to moderate UC include patients with both extensive and left-sided colitis, much of the evidence base for this statement is discussed in section 11.2.2.

Oral 5-ASA is clearly more effective than placebo for the induction of remission of mild to moderate extensive UC.[19,24] The benefit of combining oral and rectal 5-ASA was shown in a trial of 116 patients randomised to oral 5-ASA 4 g/day with a 1-g 5-ASA enema vs oral 5-ASA with a placebo enema; 64% of the combined group achieved clinical remission at Week 8 compared with 43% with oral 5-ASA alone [P = 0.03].[40] In extensive UC, as in left-sided UC, oral 5-ASA has similar efficacy to oral sulphasalazine, with a better safely profile.[24] Once-daily 5-ASA is as effective as divided doses,[24–26,30,41] irrespective of the 5-ASA formulation[24,27] and with no difference regarding adherence.[24] There may be a slight cost advantage for once-daily over three-time daily dosing.[42] At least 2 g/day oral 5-ASA is more effective than lower doses for inducing remission [RR for failure to achieve remission at Weeks 4–8 of 0.91, 95% CI 0.85–0.98],[19] whereas an initial dose of 4.8 g/day for moderately active UC may be of benefit.[24] Failure to respond to 5-ASA is an indication to start oral systemic steroids. Similarly, if a patient already receiving 5-ASA ≥ 2 g/day or IMs as maintenance therapy has a relapse, treatment with steroids can be appropriate. Current data are still insufficient to recommend 5-ASA dose escalation based solely on faecal calprotectin > 50 mg/kg, in patients in clinical remission.[43]

Evidence for the superiority of oral corticosteroids over 5-ASA comes from two early studies in active UC, which included patients with extensive colitis.[44,45] An appropriate regimen for moderately active disease is prednisolone 40 mg/day for 1 week, lowering the daily dose by 5 mg each week, resulting in an 8-week course. Shorter courses [< 3 weeks] are associated with early relapse and starting doses of prednisolone ≤ 15 mg/day are ineffective for active disease.[46]

Second-generation corticosteroids [e.g. with a colonic release mechanism and low systemic bioavailability] are an alternative to conventional preparations. Oral beclomethasone dipropionate [5 mg daily for 4 weeks, then alternate weekly for a further 4 weeks] is non-inferior with a safety profile similar to prednisone [40 mg daily for 2 weeks, then tapered by 10 mg every 2 weeks] in a recent 8-week RCT.[32] A study of 177 patients with active left-sided or extensive UC reported that oral beclomethasone dipropionate 5 mg/day had an effect similar to that of 2.4 g 5-ASA,[47]

The efficacy of oral, non-colonic release budesonide for active UC was the subject of a previous Cochrane database systematic review of three trials. Budesonide was less likely to induce clinical remission than oral 5-ASA [RR 0.72, 95% CI 0.57–0.91], with no benefit over placebo [RR 1.41, 95% CI 0.59–3.39].[33] This review has been updated,[48] supporting the use of budesonide MMX predominantly in left-sided UC, and as adjunctive treatment to 5-ASA; studies with improved power are needed to assess standard formulation budesonide in active UC. Two phase 3 induction trials of the novel MMX 9-mg budesonide preparation also failed to demonstrate a benefit over placebo in mild to moderate extensive UC, as opposed to significant efficacy in left-sided colitis.[34–36]

There is some evidence for a therapeutic benefit of probiotics when added to standard therapy to induce remission,[49] particularly VSL#3.[50] However, two meta-analyses showed significant heterogeneity between the nine and three trials evaluated, respectively. Earlier meta-analyses failed to demonstrate this beneficial effect.[51,52]

Three small RCTs have reported on faecal transplantation [FT] in active UC. More patients reached remission with FT than with water enema in one trial.[53] In another trial, there was no difference between FT using autologous faeces and that from healthy donors administered via nasoduodenal tubes.[54] FT modified patients' microbiota, which became more diverse and more similar to those of their donors. A third randomised trial has been reported as an abstract. A total of 81 patients underwent placebo enemas or FT from several donors, 5 days a week for 8 weeks; 27% patients reached steroid-free clinical and endoscopic remission at Week 8 compared with 8% with placebo [p = 0.02].[55] Open-label cross-over trials confirmed these findings. These results are encouraging and support the proof of concept for using FT to induce remission in active UC. Additional studies are warranted in order to define the best protocol [e.g. route of administration, preferred donor characteristics, frequency and duration of treatment] to optimise efficacy and ensure safety.

There is still insufficient evidence to allow firm conclusions on safety and efficacy of helminth therapy in UC.[56]

Phosphatidylcholine is a key component of the colonic mucus. Patients with UC have less phosphatidylcholine within their colonic mucus, and therefore a defective mucosal barrier function. A randomised trial has evaluated the safety and efficacy of LT-02, a pharmaceutical compound that contains at least 94% of

phosphatidylcholine.[57] This trial included 175 patients with 5-ASA-refractory UC [most of whom had left-sided or extensive colitis], randomised into four arms: one placebo and three different doses of LT-02. Although the differences in remission and endoscopic healing rates between placebo and pooled LT-02 arms were not statistically significant [$p = 0.089$ and 0.098, respectively], the rates for histological remission were 20% and 40.5%, respectively, [$p = 0.016$].

Andrographis paniculata is a herbal remedy with inhibitory activity against tumour necrosis factor [TNF], interleukin [IL]1β, and nuclear factor-kappa-B. An RCT[58] evaluating safety and efficacy in 224 patients with mild to moderate active UC demonstrated improved clinical response and endoscopic healing at Week 8 in patients who received 1800 mg of *Andrographis paniculata* as compared with placebo [$p = 0.0183$ and $p = 0.0404$, respectively].

Another RCT studied the efficacy of intra-rectal oligonucleotide TLR-9 agonist in 131 patients with active UC. The primary endpoint, remission at Week 12, was obtained in 44.4% and 46.5% of patients randomised to the experimental and placebo groups, respectively. However, the proportions of patients who reached symptomatic remission and mucosal and histological healing as well as remission at Week 4 were significantly higher in patients who received the TLR-9 agonist.[59]

Interferon-γ-inducible protein-10 [IP-10] regulates homing of immune cells within the inflammed colon, and decreases survival of gut epithelial cells. IP-10 blockade increases survival of crypt cells and reduces inflammation in animal models of UC. An RCT has assessed the safety and efficacy of eldelumab, a monoclonal antibody against IP-10 in 252 UC patients. Remission and response rates were not significantly different between experimental and placebo arms. However, trends towards higher remission and response rates were observed in patients randomised to eldelumab, particularly in anti TNF-naive patients.[60]

It is too early to recommend the use of FT, helminths, LT-02, *Andrographis paniculata*, TLR-9 agonist, or eldelumab in clinical practice. Further clinical trials are warranted.

11.2.4. Severe ulcerative colitis

ECCO statement 11F

Patients with bloody diarrhoea ≥ 6/day and any signs of systemic toxicity (pulse > 90 min^{-1}, temperature > 37.8°C, haemoglobin < 105 g/l, erythrocyte sedimentation rate [ESR] > 30 mm/h, or C-reactive protein [CRP] > 30 mg/l) have severe colitis and should be admitted to hospital for intensive treatment [EL4]. Patients with comorbidities or > 60 years old have a higher risk of mortality [EL3]

11.2.4.1. Therapeutic approach

All patients admitted with severe UC require appropriate investigations to confirm the diagnosis and exclude enteric infection.[61] Intravenous [IV] corticosteroids remain the mainstay of conventional therapy.[62] It is essential to ensure that therapeutic alternatives for the rescue of steroid-refractory disease (ciclosporin [CsA], tacrolimus, or infliximab [IFX]) are considered early [on or around Day 3 of steroid therapy] and that the decision making process is not delayed. Patients remaining on ineffective medical therapy including corticosteroids suffer a high morbidity associated with delayed surgery.[63–67] Therefore, it is essential to identify at an early stage patients likely to require colectomy, and to decide when to start rescue medical therapy. The two are not mutually exclusive and management requires careful clinical judgement.

A UK-wide audit of severe acute UC has shown that second-line medical therapy with IFX or CsA is not associated with a higher mortality. In the same study, mortality was significantly higher in individuals older than 60 and in those with comorbidities.[68]

11.2.4.2. Conventional therapy

ECCO statement 11G

Initial recommended treatment for severe active ulcerative colitis is intravenous steroids [EL1]. Monotherapy with intravenous ciclosporin [EL2] is an alternative especially in cases of serious adverse events due to steroids. All patients should receive adequate volume of intravenous fluids, and low-molecular-weight heparin for thromboprophylaxis; electrolyte abnormalities and anaemia should be corrected, if needed [EL5]. Patients are best cared for jointly by a gastroenterologist and a colorectal surgeon [EL5]

Corticosteroids are given intravenously using methylprednisolone 60 mg each 24 h or hydrocortisone 100 mg four times daily. Higher doses are no more effective, but lower doses are less effective.[4,69] Bolus injection is as effective as continuous infusion.[70] Treatment should be given for a defined period, as extending therapy beyond 7 to 10 days carries no additional benefit.[4] A systematic review of 32 trials of steroid therapy for acute severe colitis, involving 1991 patients from 1974–2006, reported an overall response to steroids [intravenous hydrocortisone, methylprednisolone, or betamethasone] of 67% [95% CI 65–69%].[4] Out of the 1991 patients, 565 [29%, 95% CI 28–31%] came to colectomy. Mortality was 1% [22/1991, 95% CI 0.7–1.6%] and none of these outcomes changed between 1974 and 2006 [$R^2 = 0.07$, $p = 0.8$]. Because of substantial heterogeneity, it was not possible to discriminate between complete and partial responsiveness to steroids.

A small RCT demonstrated that 4 mg/kg/day IV CsA monotherapy was as effective as IV methylprednisolone 40 mg/day for acute severe UC.[71] Half of all patients in another study comparing low-dose with high-dose CsA[72] also received CsA monotherapy, without the need for concomitant IV steroids. Consequently monotherapy with 2 mg/kg/day CsA [thereafter adjusted based on serum concentration] is a useful option in those patients with severe UC who should avoid steroids, such as those susceptible to steroid psychosis, patients with concomitant osteoporosis, or those with poorly controlled diabetes.

Other measures that are considered appropriate in addition to IV steroids include:

- IV fluid and electrolyte replacement to correct and prevent dehydration and electrolyte imbalance. Potassium supplementation of at least 60 mmol/day is usually necessary. Hypokalaemia or hypomagnesaemia can promote toxic dilatation;[73]
- unprepared flexible sigmoidoscopy and biopsy to confirm the diagnosis and exclude cytomegalovirus infection[74,75] which is associated with a steroid-refractory disease course[76,77] and requires appropriate treatment;[78]
- stool cultures and assay for co-existing *Clostridium difficile* toxin, which is more prevalent in patients with severe UC and is associated with increased morbidity and mortality.[68,79–86] If detected, oral vancomycin should be administered[87] and faecal microbial transplant considered.[88] Immunosuppressive therapy should be stopped if possible,[89] although this may not always be warranted;[90]

- subcutaneous prophylactic low-molecular-weight heparin to reduce the risk of thromboembolism, which is increased in patients with inflammatory bowel disease [IBD], especially during a disease flare; and is not related to other thromboembolic risk factors;[91–94]
- nutritional support if the patient is malnourished. Enteral nutrition is most appropriate and associated with fewer complications than parenteral nutrition in acute colitis [9% vs 35%].[95] Bowel rest through IV nutrition does not alter outcomes;[96]
- withdrawal of anticholinergic, anti-diarrhoeal, non-steroidal anti-inflammatory, and opioid drugs, which may risk precipitating colonic dilatation;[97–101]
- topical therapy [corticosteroids or 5-ASA] if tolerated and retained, although there have been no systematic studies in acute severe colitis;[62]
- antibiotics, only if infection is considered [such as in a first attack of short duration; after recent admission to hospital; or after travel to an area where amoebiasis is endemic], or immediately prior to surgery. Controlled trials of oral or IV metronidazole, tobramycin, ciprofloxacin, or vancomycin in acute UC have shown no consistent benefit in addition to conventional therapy;[102–104]
- blood transfusion to maintain a haemoglobin above 8–10 g/dl;[105]
- an essential multidisciplinary approach between gastroenterologists and colorectal surgeons.

11.2.5. Intravenous steroid-refractory ulcerative colitis of any extent

ECCO statement 11H

The response to intravenous steroids should be best assessed by the third day [EL3]; in non-responders, treatment options including ciclosporin [EL1], infliximab [EL1], tacrolimus [EL2], or surgery should be considered. Colectomy is recommended if there is no improvement following 4–7 days of salvage therapy [EL4]

Over the recent past, clinical trials of different salvage therapies for patients with severe UC refractory to IV steroids have been published. However, it is important that physicians do not acquiesce with the patient's understandable desire to delay surgery with inappropriate or unduly prolonged courses of therapy, as this will increase the morbidity and mortality associated with subsequent surgery.[63,64] Therefore, the important issues that must be considered and discussed with the patient include the following.

- Can one predict who will fail to respond to IV corticosteroids early, so that appropriate salvage therapy can be started in a timely fashion?
- Are the available salvage therapies [calcineurin inhibitors or IFX] equally effective? Are there subgroups of patients in whom one strategy is preferred over another?
- When should the response to salvage therapy be assessed, and if a patient fails to respond to one salvage therapy should a second therapy be commenced?

Simple, objective measures are needed to aid decision making. Factors that predict steroid failure in acute severe colitis can broadly be divided into clinical, biochemical, and radiological. Scoring systems in clinical practice use a combination of clinical and biochemical markers[3] [for a review, see[106]]. These predictive indices should mandate surgical consultation and assessment by a stoma therapist if this has not already occurred. Genetic polymorphisms have limited potential to predict disease outcomes, and cannot be used for decision making when colectomy is imminent.[107] Criteria are as follows.

- ***Clinical markers.*** A stool frequency > 12/day on Day 2 of IV corticosteroids was associated with a colectomy rate of 55%,[108] whereas a frequency > eight/day, or between three and eight together with a CRP > 45 mg/l on Day 3, predicted colectomy in 85% during that admission: known as the Oxford Criteria.[3] This index is more widely used than the Sweden Index.[109] UK IBD audit data suggest that colectomy may not be so common, occurring in only one-third of those with high scores using the Oxford criteria.[110]
- ***Biochemical markers.*** An ESR > 75 mm/h or a body temperature > 38°C on admission was associated with a 5 to 9-fold increase in the need for colectomy in a prospective study of 67 patients.[111] In this study, lack of response to steroids was predicted by < 40% reduction in stool frequency within 5 days. Nevertheless, patients [and their doctors] prefer to know an absolute estimate of the likelihood of colectomy, rather than relative measures.
- ***Radiological/endoscopic criteria.*** These include the presence of colonic dilatation > 5.5 cm or mucosal islands on a plain abdominal radiograph [both associated with colectomy in 75%].[108] A retrospective study reported that the presence of an ileus [indicated by three or more small bowel loops of gas] was associated with colectomy in 73% of patients.[112] The depth of colonic ulceration after gentle air insufflation identified 42/49 patients with deep ulcers that were associated with the need for colectomy,[113] but this is not widely used in clinical practice. Several studies have shown that endoscopic appearance at admission may also predict the need for colectomy.[114,115] In a study from Oxford, 13/14 patients with acute severe UC and an ulcerative colitis endoscopic index of severity score of 7 or 8 needed rescue therapy with IFX or CsA, colectomy, or readmission.[116] Deep ulcerations, the most severe endoscopic lesions, are located in the distal part of the colon and can be detected by a sigmoidoscopy.[115] Therefore, complete colonoscopy is not necessary, and carries an increased risk of perforation in patients with severe UC.
- ***Combined clinical, biochemical, and radiological/endoscopic criteria.*** A retrospective study of 85 patients, including 30 patients who came to colectomy, showed that patients with deep ulceration on sigmoidoscopy and Truelove and Witts' criteria had a steroid failure rate of 85%.[117] Another retrospective study of 167 patients, in whom 40% came to colectomy, enabled development of a numerical score combining mean stool frequency over 3 days, presence or absence of colonic dilatation, and hypoalbuminaemia [< 30 g/l] on admission, which was associated with the need for colectomy in up to 85%.[117]

11.2.5.1. Ciclosporin

Two RCTs have confirmed the efficacy of CsA in the treatment of severe UC.[71,118] The study by Lichtiger only included patients who had failed IV corticosteroids.[118] Nine of 11 patients failing steroids improved on 4 mg/kg/day IV CsA, whereas all nine on placebo failed to improve [RR 0.18, 95% CI 0.05–0.64]. In a further trial, 73 patients were randomised to either 2 mg/kg or 4 mg/kg of IV CsA,[72] with subsequent dose adjustment based on serum concentration. Response rates at Day 8 were similar in both groups [83% and 82%, respectively], with 9% coming to colectomy in the 2-mg/kg group and 13% in the 4-mg/kg group. Although not all patients

were failing IV corticosteroids at entry, a starting dose of 2 mg/kg/day has become the standard dose used in clinical practice. Pooling results from controlled and non-controlled clinical trials, between 76% and 85% of patients will respond to IV CsA and avoid colectomy in the short term.[71,72,118–120] Of 135 steroid-refractory patients started on CsA at 2 mg/kg in the randomised controlled Comparison Of iNfliximab and CsA in STeroid Resistant Ulcerative Colitis [CONSTRUCT] trial, colectomy rates were 25% in hospital, 30% by 3 months, and 45% by 12 months.[121] These suggest a median time to response of 4 days, which allows timely colectomy in non-responders.[72] However, the narrow therapeutic index of CsA and its side effect profile [including mortality rates of 3–4%] has limited acceptability, such that in the 2008 UK National IBD audit only 24% of patients admitted with steroid-refractory severe UC received CsA. A Cochrane review[122] concluded that numbers in controlled trials were so few that there was limited evidence for CsA being more effective than standard treatment alone for severe UC.

In two series, 58% of 76 patients[123] and 88% of 142 patients[120] who had received CsA, came to colectomy over 7 years. A single-centre review of the long-term outcome of 71 patients treated with IV CsA for severe colitis reported that successful transition to an oral thiopurine was a significant factor in preventing future colectomy [OR 0.01, 95% CI 0.001–0.09; $p < 0.0001$].[124] Successful transition to thiopurine therapy and being thiopurine-naïve at baseline have been confirmed as factors that reduce the risk of long-term colectomy in this patient group.[120,125,126] Patients who have UC refractory to adequate thiopurine therapy may therefore be less suitable candidates for CsA rescue therapy.

11.2.5.2. Tacrolimus

Tacrolimus is a calcineurin inhibitor that acts via a mechanism similar to CsA. One RCT of two tacrolimus dosing strategies has shown significant benefit over placebo in patients with UC.[127] This included 27/60 patients with severe colitis. No patient entered complete remission in any group. A partial response was seen in: 67% [4/6] of patients on tacrolimus adjusted to trough levels 10–15 ng/ml; 50% [5/10] of patients on tacrolimus adjusted to trough levels 5–10 ng/ml; and 18% [2/11] of patients on placebo (p = nonsignificant [ns]). This study was underpowered to detect a difference in patients with severe colitis. In a 2-week RCT conducted in 62 patients, oral administation of tacrolimus was significantly more effective than placebo to induce remission and endoscopic healing in patients with steroid-refractory UC.[128] A recent systematic review and meta-analysis has combined the data of these two trials and those of observational studies; it demonstrated that clinical response at 2 weeks was significantly higher with tacrolimus than with placebo [RR = 4.61, 95% CI = 2.09–10.17; $p = 0.15 \times 10^{-3}$]. Colectomy-free rates at 1, 3, 6, and 12 months were 0.86, 0.84, 0.78, and 0.69, respectively.[129] The long-term cumulative colectomy-free survival in patients with UC treated with tacrolimus has been reported to be 57% at 44 months, although this included a very heterogeneous population.[130]

11.2.5.3. Infliximab

Infliximab as a single dose [5 mg/kg] is an effective salvage therapy in patients with severe UC refractory to IV steroids. A pivotal RCT included 45 patients [24 receiving IFX and 21 receiving placebo] who were all initially treated with IV betamethasone.[131] Colectomy rates at 3 months were significantly lower in patients receiving IFX compared with placebo [7/24 vs 14/21: $p = 0.017$; OR 4.9, 95% CI 1.4–17]. Patients with less active disease who were randomised after 5–7 days of IV steroids benefited more than patients with more severe disease randomised at Day 3. An earlier pilot study and a retrospective review of IFX for acute severe colitis refractory to steroids have shown variable results.[132,133] Long-term follow-up of patients in the RCT revealed a colectomy rate at 3 years of 12/24 [50%] patients given IFX and 16/21 [76%] given placebo [without maintenance IFX being provided] [$p = 0.012$], although use of thiopurine therapy was not controlled and differed between groups.[134] A retrospective multicentre study of 211 steroid-refractory patients receiving IFX therapy reported colectomy rates of 36%, 41%, and 47% after 1, 3, and 5 years, respectively, from therapy initiation.[135] Of 135 steroid-refractory patients started on IFX in the recent CONSTRUCT study, colectomy rates were 21% in hospital, 29% by 3 months, and 35% by 12 months.[121] Case series report 20% to 75% colectomy rates after IFX for IV steroid-refractory UC.[133,136–141]

Several studies have assessed predictors of response to IFX in patients with severe and/or corticosteroid-refractory disease. At admission, high CRP level, low serum albumin, perinuclear anti-neutrophil cytoplasmic antibody seropositivity, and severe endoscopic lesions are associated with subsequent colectomy or relapse.[141,142] Short-term [i.e. Weeks 10 to 14] complete clinical response, endoscopic healing, and serum IFX level above 2.5 ug/ml at Week 14, predict colectomy-free and relapse-free survival.[88] Low serum IFX concentrations [median 2.9 ug/ml] at Week 6 has been associated with primary non-response.[143] A study found that IFX is lost in stools of patients with UC and that high faecal concentration of IFX in the first days after therapy initiation is associated with primary non-response.[144] Serum IFX levels at 2 weeks are lower in acute severe compared with moderately severe UC, although it is not known whether intensified induction is associated with better outcomes.[145]

The therapeutic regimen also appears to influence the response to IFX. A retrospective study of 83 patients suggests that patients receiving a single infusion are more likely to require colectomy at 2 months than those who receive two or more infusions [9/26 compared with 3/57; $p = 0.001$, OR = 9.53].[146] A multi-centre study concluded that a three-dose induction regimen is the treatment of choice for preventing early colectomy in severe steroid-refractory UC.[142] A small retrospective study has reported that an accelerated IFX induction strategy [median period of 24 days] was associated with a reduction in the need for early colectomy in 50 hospitalised patients with acute severe UC.[147] Finally, thiopurine-naïve status was protective from colectomy in a cohort of steroid-dependent UC patients treated with IFX plus azathioprine.[148]

11.2.5.4. Selection between calcineurin inhibitors and infliximab

The open-label CYSIF trial randomised 111 thiopurine-naive patients with severe colitis [Lichtiger score > 10] despite 5 days of IV steroids, to IV CsA 2 mg/kg/d for 8 days [levels 150–250 ng/ml] followed by 4 mg/kg/day oral therapy, or IFX 5 mg/kg at Weeks 0, 2, and 6.[149] All responders at Day 7 received oral azathioprine and tapered steroids from Day 8. The trial was initially powered to demonstrate less treatment failure with CsA than IFX between Days 7 and 98 [lack of response at Day 7, relapse between Days 7 and 98 defined as lack of steroid-free remission at Day 98, colectomy, or treatment interruption before Day 98]. Approximately 85% patients in both groups responded to treatment by Day 7. Treatment failure at Day 98 [the primary endpoint] was reported in 60% patients in the CsA arm compared with 54% patients in the IFX arm [treatment difference 6.4%, 95% CI 12–24.8%; $p = 0.49$]. The colectomy rate by Day 98 in the CsA vs the IFX group was 18% vs 21% [$p = 0.66$].[149] Serious adverse events were not significantly different between IFX and CsA [17/56 on IFX vs 9/55 on CsA]. The CONSTRUCT trial

found no significant difference regarding quality of life, colectomy, mortality rates, or the occurence of serious infections in 270 patients with acute severe steroid-resistant UC treated with CsA or IFX.[121] A meta-analysis of six retrospective studies also found comparable remission rates in patients with acute severe steroid-refractory UC receiving CsA or IFX.[150] Finally, length of hospital stay and in-hospital costs have been reduced, but total treatment cost increased since the introduction of IFX as rescue therapy compared with CsA.[151]

Therefore, the choice between options for salvage therapy should be individualised. Intravenous CsA should be avoided in patients with a low cholesterol or magnesium in view of the increased incidence of neurological side effects in this patient group. If a patient has acute severe colitis despite existing treatment with an IM at an appropriate dose and duration, it is important to consider whether current therapies maintaining long-term remission are suitably effective, recognising that new therapies may become available during the next few years.[152] Prolonged use of corticosteroids is an important risk factor for postoperative complications after colectomy.[153] One small series reported that CsA did not increase the risk of complications after colectomy.[154] In contrast, there is ongoing debate as to whether IFX increases the risk of surgical complications,[153,155–159] although one report of 108 patients found no association between rescue therapy and postoperative complications.[160]

11.2.5.5. Third-line medical therapy

In general, only a single attempt at rescue therapy with a calcineurin inhibitor or IFX should be considered before referral for colectomy. Sequential rescue therapy has been assessed by a systematic literature review that included 10 studies and 314 participants.[161] Short-term response and remission rates were 62.4% and 38.9%, respectively. Colectomy rates were 28.3% at 3 months and 42.3% at 12 months. Adverse events occurred in 23% of patients, including serious infections in 6.7% and mortality in 1%. These results may suggest that the risk of sequential therapy in steroid-refractory UC is acceptable. However, the evidence is poor. No recommendation for [or against] the use of sequential rescue therapy can be made on the basis of the available data. Third-line medical therapy can be considered in specialist referral centres in highly selected cases, after careful discussion between the patient, gastroenterologist, and colorectal surgeon.

Additional antibiotic therapy has been assessed in an open-label study based upon 30 UC patients. Treatment with amoxicillin, tetracycline, and metronidazole for 2 weeks appeared to be effective in steroid-refractory UC[162;] however, an earlier, blinded RCT in 39 patients with acute severe colitis demonstrated no benefit from metronidazole and tobramycin.[103]

11.2.6. *Toxic dilatation and complications of severe ulcerative colitis*

11.2.6.1. Toxic megacolon

Toxic megacolon is defined as total or segmental non-obstructive dilatation of the colon ≥ 5.5 cm, associated with systemic toxicity.[97] Risk factors include hypokalaemia, hypomagnesaemia, bowel preparation, and the use of anti-diarrhoeal therapy.[97] Earlier diagnosis of severe colitis, more intensive medical management, and earlier surgery have reduced the incidence and mortality of toxic megacolon complicating UC. In addition to IV hydrocortisone, empirical treatment with oral vancomycin should be considered until stool is confirmed negative for *C. difficile* toxin. An opinion from an experienced colorectal surgeon is required on the day of admission. There is a limited window of opportunity for medical treatment to work and, without rapid improvement, early colectomy will be necessary.

11.2.6.2. Perforation, haemorrhage and thromboembolism

Perforation is the most serious complication of acute severe colitis and can be associated with inappropriate total colonoscopy or toxic dilatation where colectomy has been inappropriately delayed. It carries a mortality of up to 50%.[97] Other complications include massive haemorrhage, and thromboembolism including cerebral sinus thrombosis.[91,92]

11.2.6.3. Long-term outcome of severe colitis

There is evidence that achieving complete clinical remission during the index hospital admission improves long-term outcome and delays the need for colectomy.[163] Patients needing CsA for acute severe colitis, who are naïve to IM therapy and successfully transition to thiopurine maintenance therapy, are less likely to require colectomy during long-term follow-up.[120,124,125] Unsurprisingly, irrespective of whether CsA or IFX is used as salvage therapy, patients with clinical, biochemical, or endoscopic evidence of more severe disease at presentation are more likely to require colectomy.[164]

11.2.7. Refractory proctitis and distal colitis

It is important to identify the aetiology of refractory disease. One explanation is that the disease is refractory to medication being prescribed. However, alternative explanations include:

1] poor adherence to prescribed therapy;
2] delivery of an inadequate concentration of the active drug to the inflamed mucosa;
3] unrecognised complications [such as proximal constipation or infection];
4] inappropriate diagnosis [e.g. irritable bowel syndrome, Crohn's disease [CD], mucosal prolapse, cancer].

Therefore, the initial step is to review current symptoms, treatment history, and adherence to medical therapy. This should be followed by reassessment of the diagnosis by stool culture, endoscopy, and biopsy. The next step is to ensure that conventional therapy [sections 11.2.1 and 11.2.2] has been used appropriately. Attention should focus on the formulation of topical therapy and whether it was used in conjunction with an adequate dose of oral therapy. An abdominal X-ray can be useful to diagnose proximal constipation, since abnormal intestinal motility induces proximal colonic stasis in patients with distal colitis, which may affect drug delivery.[165] If there is visible faecal loading, a laxative should be considered.

Patients with endoscopically documented active distal colitis or proctitis, who fail oral corticosteroids combined with oral and rectal 5-ASA therapy, have refractory disease. Therapeutic options include admission for IV steroid therapy, which has been reported to induce remission in a high proportion of patients.[166] Alternatively, there is open-label evidence, often from retrospective case reviews, supporting the use of salvage medical therapies such as oral or rectal CsA, oral or rectal tacrolimus, or IFX.[167–171]

If disease persists, surgery is likely to be the outcome. RCTs have suggested a benefit of short-chain fatty acid enemas,[172,173] although difficulties with production and availability limit their use. Small open-label trials have suggested benefit from alternative topical therapies such as lidocaine enemas, arsenic suppositories, epidermal growth factor enemas, alicaforsen enemas, and transdermal nicotine patches.[174–178] Retrospective cohort studies have suggested that appendicectomy may improve patients with refractory proctitis.[179–182] Up to 10% of patients who have a colectomy for refractory UC only have distal colitis. The outcome of colectomy and pouch formation for distal UC is usually good.[183]

11.3. Treatment according to the course or behaviour of disease

11.3.1. Steroid-dependent active ulcerative colitis

ECCO statement 11I

Patients with steroid-dependent disease should be treated with a thiopurine [EL2], anti-TNF [EL1] [preferably combined with thiopurines, at least for infliximab [EL2]], vedolizumab [EL2], or methotrexate [EL2]. In case of treatment failure, second-line medical therapy with an alternative anti-TNF [EL4], vedolizumab [EL2], or colectomy [EL5] should be considered

Azathioprine is significantly more effective than 5-ASA at achieving clinical and endoscopic remission in steroid-dependent UC. In an open-label trial, 72 patients were randomised to receive azathioprine 2 mg/kg/day or oral 5-ASA 3.2 g/day, in addition to prednisolone 40 mg/day;[184] 53% of patients receiving azathioprine achieved steroid-free clinical and endoscopic remission after 6 months compared with 21% with 5-ASA [OR 4.78, 95% CI 1.57–14.5]. In addition, an open label observational cohort study in 42 steroid-dependent patients reported steroid-free remission with azathioprine at 12, 24, and 36 months of 55%, 52%, and 45%, respectively.[185] These studies suggest that thiopurines are efficacious in patients who flare when steroids are withdrawn.

Steroid-free remission was a secondary endpoint of the pivotal trials of anti-TNF in UC. For IFX, the ACT-1 and ACT-2 trials each included 364 patients with endoscopically confirmed moderate/severely active colitis despite treatment with corticosteroids and/or thiopurines [ACT-1], or with corticosteroids and/or thiopurine and/or 5-ASA [ACT-2]. Participants were all anti-TNF naïve, and randomised to receive placebo or IFX; 56% of patients entered the combined studies on steroids, including 38% who were taking the equivalent of ≥ 20 mg/day prednisolone. For those participants who were receiving corticosteroids at baseline, 21.5% of those receiving IFX reached steroid-free remission by Week 30, compared with 7.2% of those receiving placebo [p = 0.007].[186] Cohort but not RCTs have reported on the effectiveness of IFX in steroid-dependent patients.[148,187]

In ULTRA 2, the pivotal RCT of adalimumab in patients with moderate to severe UC, 494 adult patients with endoscopically confirmed moderate/severely active colitis despite treatment with corticosteroids and/or thiopurines, were randomised to receive 160 mg adalimumab at Week 0, 80 mg at Week 2, and then 40 mg every other week from Week 4.[188] A total of 59% of participants entered the study receiving corticosteroids and 40% of participants had a history of previous anti-TNF failure. In all, 31% of participants who received adalimumab were steroid-free at Week 16 compared with 16% allocated to placebo [$p < 0.05$]. At Week 52, 13.3% of participants in the adalimumab group, who had been receiving corticosteroids at baseline, were in steroid-free remission compared with 5.7% in the placebo group [p = 0.035].

The efficacy of golimumab in patients with endoscopically confirmed moderate/severely active UC refractory to steroids and/or 5-ASA and/or thiopurines was established in the PURSUIT trials.[189,190] Participants were all anti-TNF naïve. In these studies, assessment of induction and maintenance were uncoupled, with a placebo-controlled randomised series of induction trials across different golimumab dosing regimens. In the PURSUIT-M trial, 464 patients showing evidence of response to induction therapy at Week 6 were then re-randomised to receive maintenance treatment with either placebo or golimumab; 51.5% of patients entered PURSUIT-M on corticosteroids, including 36% on ≥ 20 mg/day prednisolone. Specifically for those patients entering PURSUIT-M receiving corticosteroids, 34.4% of those treated with golimumab and 20.7% who received placebo achieved steroid-free remission by Week 54 [p = 0.024].[189]

Taken together, all these anti-TNF agents are more effective than placebo in obtaining and maintaining steroid-free remission in those receiving corticosteroids at baseline. An important consideration is the utility of combination therapy with anti-TNF and IM. The UC-SUCCESS trial suggests that a combination of IFX plus azathioprine is more effective than using IFX alone.[191] This was a 16-week, randomised, double-blind, controlled trial in biologic-naïve patients with moderate to severe UC, who were largely naïve to IM. Corticosteroid-free remission at Week 16 was achieved by 39.7% [31 of 78] patients receiving IFX/azathioprine, compared with 22.1% [17 of 77] receiving IFX alone [p = 0.017] and 23.7% [18 of 76] receiving azathioprine alone [p = 0.032]. Combination therapy within RCTs has not been assessed for adalimumab or golimumab or in IM-exposed patients [see section 11.3.3].

Another important question is the efficacy of a second anti-TNF after the failure of a first one. In ULTRA-2, the co-primary endpoint of clinical remission at Week 8 was not met in the TNF-failure population. The other co-primary endpoint of clinical remission at Week 52 was achieved in this population [10.2% on adalimumab vs 3.0% on placebo, p = 0.039], although the difference from placebo for this, as well as several other secondary endpoints, was smaller in the TNF-failure population than in the TNF-naïve population. The secondary endpoint of corticosteroid-free remission at Week 52 in those patients receiving steroids at baseline was not met in the TNF-failure population. A recent meta-analysis has addressed the clinical success rate of a second anti-TNF after the failure of a first one, in patients exposed [or not] to steroids. Eight UC studies were included, all of them switched IFX to adalimumab. The response rate ranged from 23% to 92%, whereas the remission rates varied between 0% and 50%.[192] However, due to heterogeneity in study design, it was not possible to estimate the pooling efficacy through a formal meta-analysis.

Steroid-free remission was also a secondary endpoint of the pivotal trial of vedolizumab in endoscopically confirmed moderate/severely active UC, GEMINI-1.[193] Similar to the PURSUIT trials already discussed, GEMINI-1 included an induction trial of 374 patients, with Week 6 responders then re-randomised to vedolizumab or placebo during a maintenance phase. Additional induction responders for the randomised maintenance phase were drawn from a second cohort who had received open-label vedolizumab induction therapy.[193] Participants were refractory to steroids and/or thiopurines and/or anti-TNF therapy. A total of 53.7% of patients in the GEMINI 1 trial were receiving glucocorticoids at study baseline and 48% had failed previous anti-TNF therapy. In those who were receiving corticosteroids at baseline, and who responded to induction therapy and were re-randomised to vedolizumab, 38.5% achieved steroid-free remission at Week 52, compared with 13.9% re-randomised to placebo [$p < 0.001$]. Neither concurrent treatment with corticosteroids, IMs, nor previous treatment with TNF antagonists affected the efficacy of vedolizumab in the induction or maintenance phases, suggesting that patients with steroid-dependent disease or previous anti-TNF failure have a comparable outcome. A German cohort study reported that 25% of UC and CD patients were in clinical remission by 14 weeks.[194] Data on the use of anti-TNF after primary failure of vedolizumab are currently not available.

Methotrexate has been studied in a multicentre trial including 111 patients with steroid-dependent UC.[195] The primary endpoint, steroid-free remission at Week 16 [defined as a Mayo score ≤ 2 with no sub-score > 1 and complete withdrawal of steroids], was achieved in 31.7% patients assigned to methotrexate [MTX] and 19.6% patients who received placebo [$p = 0.15$]. The rate of steroid-free clinical remission at Week 16 [defined as a Mayo score ≤ 2 with no sub-score > 1] was 41.7% for MTX and 23.5% for placebo [$Pp = 0.04$]. This trial failed to show that parenteral MTX is beneficial for induction of steroid-free remission in UC. However, MTX induced clinical remission without steroids at Week 16 more frequently than placebo, and was associated with better control of disease-related symptoms.

11.3.2. Oral steroid-refractory active ulcerative colitis

ECCO statement 11J

Moderate disease refractory to oral steroids should be treated either with intravenous steroids [EL4] or anti-TNF [EL1] preferably combined with thiopurines, at least for infliximab [EL2], vedolizumab [EL2], or tacrolimus [EL2]. Second-line medical therapy with a different anti TNF [EL4] or vedolizumab [EL2] may be an option; colectomy should also be considered

In patients with active steroid-refractory UC, other causes of persistent symptoms such as coexistent cytomegalovirus, *C. difficile*-associated disease, or cancer, should be considered. Intravenous steroids are still an option in patients with confirmed, active steroid-refractory UC, even though patients with moderately active UC are preferably not treated in hospital. Intravenous steroids have been suggested to be more efficient in a retrospective study involving 110 episodes of disease refractory to oral steroids.[109,196] However, almost half of the patients developed early steroid-dependency in this study.

As already discussed, anti-TNF therapy and vedolizumab have shown clear evidence of benefit in patients with corticosteroid dependency, through achievement of corticosteroid-free remission in patients receiving steroids at baseline.[186,188–190,193,197] All the pivotal trials included corticosteroid-refractory disease as a potential inclusion criterion and demonstrated efficacy of biologic therapy across a range of endpoints. However, although rates of corticosteroid usage at baseline and some dose thresholds were reported, steroid doses used before inclusion may have been suboptimal, and it is not always possible to differentiate all steroid-dependent or steroid-refractory patients and assess trial outcomes separately for these groups across all trials.

Tacrolimus has been studied in two randomised double-blind controlled trials. In the first trial, 60 corticosteroid-refractory UC patients were randomly assigned to receive oral tacrolimus at high serum trough [10–15 ng/ml; $n = 19$] or low serum trough [5–10 ng/ml; $n = 21$] levels, or placebo [$n = 20$].[127] Two weeks after treatment, the clinical response rates were 68.4% and 38.1% in the high-trough and low-trough groups, respectively, and 10.0% in the placebo group. An RCT that included 62 patients with corticosteroid-refractory, moderate to severe UC[128] assessed oral tacrolimus, with serum trough levels fixed at 10–15 ng/ml; a similar result to the first study was obtained, with clinical response rates of 50.0% in the tacrolimus group and 13.3% in the placebo group at Week 2 [$p = 0.003$]. Several retrospective cohort studies have been reported.[171] A recent systematic review and meta-analysis has reported that clinical response at 2 weeks was significantly higher with tacrolimus than with placebo [RR 4.61, 95% CI 2.09–10.17; $p = 0.15 \times 10^{-3}$]. Colectomy-free rates at 1, 3, 6, and 12 months were 0.86, 0.84, 0.78, and 0.69, respectively.[129] An open study of 100 patients with moderate to severe UC compared tacrolimus and anti-TNF, with similar efficacy and safety outcomes.[198]

Two phase 3 trials have studied the efficacy of oral tofacitinib [a janus kinase inhibitor, 10 mg twice daily] as induction therapy in 1139 patients with active, moderate to severe UC.[199] Included patients had failed corticosteroids, azathioprine, or anti-TNF [53–58% of patients were previously exposed]. Remission at Week 8 was achieved in 18.5% and 16.6% in the tofacitinib arms vs 8.2% and 3.6% in the placebo arms; both differences were statistically significant. Increased serum levels of cholesterol and creatine kinase were observed with tofacitinib. It has not yet been licensed for use in Europe.

Another recent randomised phase 2 trial using ozanimod [a modulator of the sphingosine-1-phosphate receptor subtypes 1 and 5] showed that 16% of patients who received ozanimod 1 mg/day, and 6% of patients who received placebo, reached clinical remission at Week 8 [$p = 0.048$].[200] Larger studies are needed to study the efficacy and safety of ozanimod in moderate to severe UC.

11.3.3. Immunomodulator-refractory ulcerative colitis

ECCO statement 11K

Patients with moderate colitis refractory to thiopurines should be treated with anti-TNF [EL1], preferably combined with thiopurines, at least for infliximab [EL2], or vedolizumab [EL2]. In case of treatment failure, a different anti-TNF [EL4] or vedolizumab [EL2] should be considered, and colectomy recommended if further medical therapy does not achieve a clear clinical benefit [EL5]

IM-refractory disease is best assessed by endoscopy and biopsy to confirm the diagnosis and exclude complications. For active UC that is refractory to thiopurines, other causes of persistent symptoms include coexistent cytomegalovirus or *C. difficile*-associated disease. A therapeutic strategy to induce and maintain steroid-free remission should be discussed with the patient. In the absence of contraindications, biologic therapy should be considered. Infliximab, adalimumab, golimumab, and vedolizumab have all been evaluated for use in UC refractory to thiopurines. Tofacitinib has also been shown to be effective in this patient population.[199,201]

The ACT 1 and ACT 2 trials included 334/728 [46%] patients with active disease despite concomitant IM therapy.[186] Infliximab at either dose [5 or 10 mg/kg] achieved clinical remission in a significantly greater proportion of patients at Week 8 than placebo, although the response for the subgroup of IM-refractory patients was not reported. A Cochrane database systematic review, of seven trials of IFX for treating patients with moderate to severe UC refractory to corticosteroids and/or IMs, concluded that IFX [three intravenous infusions at 0, 2, and 6 weeks] was more effective than placebo at inducing clinical remission at Week 8 [RR 3.22, 95% CI 2.18–4.76].[202] This review did not report the benefit in the patient subgroup refractory to IM therapy.

In the ULTRA-1 trial demonstrating superiority of adalimumab over placebo for the induction of remission of UC [see statements 11G and 11H], 154 of the 390 [39%] patients were receiving concomitant immunosuppression at baseline.[203,204] In patients receiving

concomitant IM without corticosteroids, adalimumab induced clinical remission at Week 8 in 8/53 [15.1%] patients, compared with 0/18 patients receiving placebo [0%]; for those receiving concomitant IM with corticosteroids, Week 8 remission rates were 6/49 [12.2%] for adalimumab compared with 2/34 [5.9%] for placebo. In the ULTRA-2 trial, 173 of 494 patients [35%] were on concomitant immunosuppression.[188] A separate subgroup analysis for these patients was not reported.

Adalimumab 160 mg/80 mg/40 mg alternate weekly induced clinical remission at Week 8 in 8/53 [15.1%] patients compared with 2/52 patients receiving placebo [3.8%]. A prospective cohort study of 53 patients receiving either IFX or adalimumab for moderately active UC reported short-term clinical response in 88.7% patients with no significant difference in the response rates between drugs.[205] All patients recruited had failed or were intolerant to IM therapy, although only 5/25 patients treated with adalimumab and 15/28 patients treated with IFX were taking concomitant IM therapy at baseline.

The PURSUIT trial of golimumab included 31.2% of patients with moderate to highly active disease, taking thiopurines.[189] Concurrent treatment with IMs did not affect efficacy.

A common question is whether to continue an IM when starting anti-TNF therapy in patients with IM-refractory colitis. The UC-SUCCESS trial[191] only included patients with steroid-refractory disease, and patients were required to be either IM naïve [the case in 90%] or last exposed to IM > 3 months preceding inclusion. Hence the cohort represented a largely IM-naïve population, from which it may not be possible to draw direct extrapolation to guide therapy in IM-refractory patients. The recommendation given for the combined use of IFX and thiopurines in IM-refractory patients is therefore based on indirect data showing that concomitant immunosuppression might reduce antibody production and/or increase trough levels of IFX and efficacy of treatment.[206,207] Neither subgroup analysis of clinical trials nor retrospective analysis of pharmacokinetic samples would appear to support a similar conclusion for adalimumab or golimumab.[189,208]

The GEMINI 1 trial included 17.8% of patients taking IMs and 16.6% of patients taking glucocorticoids and IMs.[193] Subgroup analysis for response to induction therapy did not report the total cohort of previous -IM failures, but only those with previous IM failure with no history of anti-TNF failure, in whom a trend towards benefit for vedolizumab compared with placebo was observed but did not reach statistical significance [49% vs 34.5%; $p = 0.08$]. Subgroup analysis in the maintenance study, using this same definition of previous IM failure without a history of anti-TNF failure, showed a significantly higher remission rate at 1 year for those induction responders who were re-randomised to vedolizumab maintenance therapy [44.6% for those dosed with vedolizumab every 8 weeks [$p = 0.001$ vs placebo]; 50% for those dosed every 4 weeks [$p < 0.001$ vs placebo]; 18% for those on placebo]. Ongoing concomitant treatment with IMs did not substantially affect the efficacy of vedolizumab.

As described in section 11.3.1, data on second-line therapy with a second anti-TNF after failure of an initial anti-TNF are limited [see statement 11G]. For vedolizumab, GEMINI-1 included 48% of patients with a history of previous anti-TNF therapy; in exploratory subanalyses, outcomes were not significantly different in this group of patients, suggesting that patients with a history of anti-TNF failure may have a comparable outcome to anti-TNF naïve patients.

The OCTAVE 1 and 2 trials of tofacitinib[199] included patients who had failed azathioprine. Therefore, tofacitinib may be an option in patients with moderate to severe UC refractory to thiopurines, once it has been approved by the European Medicines Agency.

There is case series evidence to support the use of tacrolimus,[209,210] but no controlled clinical trial has included this patient group. Careful discussion with the patients is required as to the relative risks and benefits of immunosuppressive therapy compared with colectomy, which may be a more appropriate option for some patients.

11.4. Biosimilars

The currently available infliximab biosimilars have molecular structures very close to that of the reference product. Both biosimilars and the reference product [IFX] have similar physical and chemical properties, biological activity, pharmacokinetics, and animal and healthy volunteers' toxicity. Two phase 3 trials have shown that the IFX biosimilars and IFX have similar efficacy, toxicity, and immunogenicity in rheumatoid arthritis and ankylosing spondyloarthritis.[211,212] Open-label studies suggest that IFX biosimilars are efficient in UC.[213–217] Comparative phase 3 trials are progressing. Based on preclinical and clinical data, the European Medicines Agency has allowed the IFX biosimilars to be marketed in rheumatoid arthritis, spondyloarthritis, UC, and CD. The ECCO position statement on biosimilars has recently been updated.[218]

Section 12. Maintenance of Remission

12.1.1. Goal of maintenance therapy

ECCO statement 12A

The goal of maintenance therapy in ulcerative colitis is to maintain steroid-free remission, defined clinically [EL1] and endoscopically [EL2]

The endpoint that matters most to patients is steroid-free clinical remission. Clinical relapse, defined by an increase in stool frequency and recurrence of rectal bleeding, and confirmed by endoscopy, is not the only approach to the evaluation of maintenance therapy, and several pivotal trials have addressed other endpoints. In particular, recent trial designs have tended to assess both induction and subsequent maintenance in the same study. Using this approach, clinical response to induction therapy has been defined as a primary endpoint, with the efficacy of maintenance therapy evaluated as a secondary endpoint,[186] or as a co-primary endpoint,[219] or as an endpoint for evaluation solely in those who have responded to and undergone re-randomisation at the end of induction therapy.[189,193] Additionally, the definition of remission has varied, complicating efforts to make meaningful comparisons between different trials.[220,221]

12.1.2. Impact of remission on long-term outcome

ECCO statement 12B

Long-term maintenance treatment is recommended for almost all patients [EL1]. Intermittent therapy is acceptable insome patients with proctitis [EL3]

Long-term prognostic studies show low rates of remission [< 50% of patients]. Ongoing treatment with 5-ASA, thiopurines, or biologic therapy increases long-term remission rates.[19,222,223] A stringent endpoint for remission [clinical plus endoscopic remission] is related to longer duration of remission. For example, an endoscopic score of 0

[defined as complete mucosal healing] applied to a post-hoc analysis of the ACT 1 and 2 trials, revealed that patients with healing at Week 8 had a 4-fold increased likelihood of remission at Week 30 of IFX treatment.[224,225] Whereas mucosal healing correlates with improved clinical outcomes,[225,226] it has not been demonstrated that treatment approaches specifically targeting mucosal healing as an endpoint are themselves associated with improved clinical outcomes, and it is possible that patients achieving mucosal healing in such studies represent a subgroup with less aggressive disease.

12.1.3. Risk factors for relapse

ECCO statement 12C

Choice of maintenance treatment is determined by disease extent [EL1], disease course [frequency and intensity of flares] [EL5], failure and adverse events of previous maintenance treatment [EL5], severity of the most recent flare [EL5], treatment used for inducing remission during the most recent flare [EL5], safety of maintenance treatment [EL1], and cancer prevention [EL2]

Few prospective studies have assessed risk factors for relapse in patients with inactive UC.[227–231] In one study of 92 patients, a shorter duration of current remission and a higher relapse frequency were predictive of further relapse.[227] In a study of 64 patients, the frequency of previous relapses, extra-intestinal manifestations, and a low-fibre diet were independent variables associated with a higher risk of relapse.[228] In a study of 74 patients including various biomarkers and clinical measures, younger age, multiple previous relapses [for women], and basal plasmacytosis on rectal biopsy specimens, were independent predictors of relapse.[229] This study did not confirm the 2-fold increase in relapse rate in those with persisting active inflammation [polymorphonuclear leukocytes in the rectal mucosa] observed in two earlier histopathology studies.[232,233] Histology grade has recently been reported as having the strongest association with the risk of clinical relapse in patients with UC who are in clinical remission.[234] Adherence to medical therapy still appears to be a governing factor associated with relapse, since the risk of relapse was more than 5-fold higher [OR 5.5, 95% CI 2.3–13.0] among 99 patients who collected < 80% of their prescriptions for maintenance 5-ASA.[235]

Patients with disease requiring steroids probably have a different outcome compared with the overall population of patients with UC. In a population-based study, the outcome of 183 patients with UC diagnosed between 1970 and 1993 was analysed 1 year after a first course of steroids.[236] Among the 63/183 patients treated with corticosteroids, 49% had a prolonged response, 22% were steroid dependent, and 29% came to colectomy, but only 3/183 were treated with thiopurines.

Both mucosal healing and a previous episode of acute severe colitis impact on the key outcome of colectomy. In a population-based study from south east Norway, 423/519 patients with UC were available for analysis at 10 years [53 had died and 43 were lost to follow-up].[237] The cumulative colectomy rate after 10 years was 9.8% [95% CI 7.4–12.4%]. Initial presentation with extensive colitis or acute severe colitis tripled the risk of subsequent colectomy [HR 3.57, 95% CI 1.60–7.96], whereas age ≥ 50 years at diagnosis reduced the risk by 3-fold [HR 0.28, 95% CI 0.12–0.65]. Relapsing disease occurred in 83%, but half [48%] of the patients were relapse free during the last 5 years. Mucosal healing by 12 months from diagnosis was associated with a lower colectomy rate [2% vs 8% without mucosal healing, p = 0.02].[237] Meta-analysis of clinical predictors of colectomy in patients with UC identified male gender, extensive disease, need for corticosteroids, non-smoking status, and hospitalisation for UC as significantly associated with colectomy risk.[238] Recent systematic review confirms an association between mucosal healing and colectomy avoidance, steroid-free remission, and clinical remission.[225]

12.2. Medications for Maintenance of Remission

ECCO statement 12D

Options for a stepwise escalation of maintenance therapy include dose escalation of oral/rectal aminosalicylates [EL1], the addition of thiopurines [EL2], and anti-TNF therapy or vedolizumab [EL1]

12.2.1. Aminosalicylates

ECCO statement 12E

Mesalamine compounds are the first-line maintenance treatment in patients responding to mesalamine or steroids [oral or rectal] [EL1]. Rectal mesalamine is first-line maintenance in proctitis and an alternative in left-sided colitis [EL1]. A combination of oral and rectal mesalamine may be used as second-line maintenance treatment [EL1]

12.2.1.1. Oral 5-ASA

A Cochrane meta-analysis showed that the relative risk of failure to maintain clinical or endoscopic remission [defined by withdrawal or relapse] for oral 5-ASA vs placebo was 0.69 [95% CI 0.62–0.77].[24] Numerous RCTs designed to evaluate the efficacy of oral 5-ASA, including sulphasalazine, various 5-ASA formulations, olsalazine, and balsalazide, for maintaining remission have been conducted.[239–248]

12.2.1.2. Rectal 5-ASA

Several RCTs have compared rectal 5-ASA in various formulations and regimens with placebo for maintenance of remission in distal UC.[249–255] At 12 months, failure to maintain clinical or endoscopic remission was 20–48% in the active arms compared with 47–89% in the placebo arms. In all but one of the trials, the differences in failure to maintain remission between active and placebo groups were statistically significant. A meta-analysis, that included four placebo-controlled trials, showed a superiority of rectal 5-ASA over placebo for maintenance of remission at 1 year [RR 2.22, 95% CI 1.26–3.90].[256]

12.2.1.3. Combining oral and topical 5-ASA therapy

There have been two RCTs comparing combination treatment with oral 5-ASA plus intermittent 5-ASA enema with oral 5-ASA alone, for maintaining remission. Remission rates were higher in patients receiving the combination.[252,257]

Oral or rectal 5-ASA is superior to placebo in maintaining remission in UC. Rectal 5-ASA has equivalent or slightly superior efficacy to oral 5-ASA in distal UC. The combination of oral 5-ASA and intermittent rectal 5-ASA appears to provide further benefit.

Although the long-term tolerance and acceptability of rectal treatment is variable, [258] adding rectal therapy is a treatment option for patients who have relapsed on oral 5-ASA alone, although adherence to prescribed therapy should be addressed. A valid alternative is the use of formulations that have been demonstrated to provide significant levels of 5-ASA in the distal colon. This has been demonstrated with good efficacy for newer 5-ASA granule formulations and MMX-mesalamine that are superior to conventional ileal-release 5-ASA in distal UC.[13,246,259]

ECCO statement 12F

The effective dose of oral mesalamine to maintain remission is 2 g/day [EL1]. For rectal treatment, 3 g/week in divided doses may be sufficient. Once-daily administration of mesalamine is the preferred dosing regimen [EL2]. Although sulphasalazine is equally or slightly more effective [EL1], oral mesalamine preparations are preferred to reduce toxicity. All preparations of oral mesalamine are effective [EL1]

12.2.1.4. Dose-response effect

A clear dose-response for maintenance of remission with 5-ASA has not been established. No difference was found in relapse rates at 1 year with 5-ASA 1.2 g/day compared with 2.4 g/day.[260] Patients taking the higher dose were in remission for longer than those on the lower dose [median time in remission of 175 days vs 129 days, $p < 0.001$]. For those with extensive UC, however, the benefit of the higher dose was more prolonged [143 days vs 47 days, $p < 0.005$]. When the results for patients in remission at 12 months were analysed after stratifying for frequently relapsing disease [> 3 relapses per year] vs less frequent relapses, 2.4 g/day also performed significantly better than 1.2 g/day [75% vs 33%, respectively]. Systematic review of seven RCTs[19] has confirmed greater benefit for doses of at least 2 g/day [studies included mesalamine, olsalazine, sulphasalazine, and balsalazide] as compared with lower doses. Higher doses [≥ 2 g/day] are not associated with more adverse events.[261] Recent Canadian guidelines recommend 2 g/day 5-ASA as maintenance therapy for UC patients in remission.[262] It is possible that patients who required higher doses of oral 5-ASA to induce remission or those with frequently relapsing disease require higher maintenance doses as well, but at present there is no robust evidence to support this.[263] There are also no data supporting a dose-response relationship with rectal 5-ASA for maintaining remission in distal UC, and no more than 1 g/day is required.

Several studies[25,241,242,246,264] have compared different dosing regimens for various 5-ASA formulations. Without exception, they have all concluded that once-daily administration is at least as effective as twice or three times daily administration. The comparable efficacy between once-daily and divided dosing regimens in the maintenance treatment of UC, obtained with different 5-ASA formulations, suggests that this effect is generic to 5-ASA rather than compound-specific. Interestingly, once-daily administration of 5-ASA has not been found to be associated with an increased rate of side effects in any of these studies. In conjunction with the likely improvement in patient convenience and adherence to treatment, this makes once-daily administration of 5ASA compounds the first choice in maintenance therapy in patients with UC.

12.2.1.5. Comparison of oral 5-ASA formulations

A Cochrane meta-analysis[24] compared sulphasalazine and different 5-ASA formulations. The odds ratio was 1.14 [95% CI 1.03–1.27] suggesting greater therapeutic effectiveness for sulphasalazine, although not when restricting analysis to those studies reporting endpoints at 12 months [RR 1.10, 95% CI 0.98–1.23]; nor when excluding olsalazine [RR 1.08, 95% CI 0.92–1.26], a drug limited by adverse events. Overall, adverse events of 5-ASA are no different to sulphasalazine [RR 1.07, 95% CI 0.82–1.40]. However, most trials enrolled sulphasalazine-tolerant patients, which would have minimised sulphasalazine-related adverse events. No significant differences in efficacy or adverse event rates were found analysing pooled studies comparing different 5-ASA formulations.

12.2.1.6. Adherence to 5-ASA treatment

Adherence to 5-ASA therapy improves outcome in patients with UC. The adherence rate in 94 outpatients taking 5-ASA with clinically quiescent UC for at least 6 months was 40% and the median amount of medication dispensed per patient was 71% [8–130%] of that prescribe.d[265] Logistic regression found that a history of four or more prescriptions or male gender increased the risk of non-adherence. In a pilot study, patients were randomised to receive either once-daily or conventional [two or three times daily] 5-ASA for maintenance of remission in UC.[266] After 6 months, patients in the once-daily arm appeared more satisfied with their regimen and consumed more medication than those in the conventional arm [90% vs 76%; $p = 0.07$]. The authors concluded that once-daily oral formulations of 5-ASA were likely to be a better therapeutic option with comparable efficacy and improved adherence. An investigator-blinded study of 362 patients randomised to receive ethylcellulose-coated 5-ASA, 2 g once daily or 1 g twice daily, showed a 12% better remission rate at 1 year [73.8% vs 63.6%, respectively] in the once-daily dose group.[241] Patient questionnaires showed significantly greater compliance [$p < 0.05$] and acceptability [$p < 0.001$] in the once-daily group. Given the comparable efficacy between once-daily and divided dosing regimens for the treatment of active UC with other 5-ASA formulations, this effect is likely to be generic rather than compound-specific.[241,242,246,264]

12.2.2. Thiopurines

ECCO statement 12G

Thiopurines are recommended for: patients with mild to moderate disease activity who have experienced early or frequent relapse while taking mesalamine at optimal dose or who are intolerant of mesalamine [EL5]; patients who are steroid-dependent [EL2]; and patients responding to ciclosporin or tacrolimus [EL3]

12.2.2.1. Efficacy of thiopurines for maintenance of remission

Several RCTs evaluating the efficacy of thiopurines (azathioprine and mercaptopurine [MP]) for maintenance of remission in UC have been performed.[184,267–272] In a Cochrane meta-analysis, seven of these studies on 302 patients were considered.[222] The study quality was judged as generally poor and the evidence for using thiopurines in UC was weaker than for CD. Azathioprine was superior to placebo on the basis of four trials [RR for failure to maintain remission 0.68, 95% CI 0.54–0.86]. The results were similar when limited to patients with successful induction of remission [data available for two studies]. There was no clear evidence of a dose-response effect for co-medication with 5-ASA in these studies. Adverse effects occurred in 9/115 patients receiving azathioprine, including acute pancreatitis [three cases] and bone marrow suppression [five cases].

Evidence to support the use of thiopurines for UC also comes from retrospective series.[273–278] In the Oxford series, the overall remission rate in 346 patients with UC who were treated with azathioprine was 58%, but increased to 87% among patients receiving therapy for more than 6 months. The proportion of patients in remission at 5 years was 62% when applying a strict definition of relapse, or 81% allowing for a brief relapse with a short corticosteroid course. The median time to relapse after stopping azathioprine was 18 months.[279] A recent retrospective study reported relapse rates of 36% by 3 years following stopping thiopurines in patients in sustained remission, particularly in patients with extensive UC, evidence of biological disease activity at the time of cessation, or a short duration of thiopurine treatment.[280]

12.2.2.2. Thiopurines after calcineurin inhibitors for induction of remission

Calcineurin inhibitors [CsA, tacrolimus] are rescue therapy options for steroid-refractory UC. Since they are best discontinued within 6 months because of side effects, these agents are generally proposed as induction therapy until slower-acting IMs become effective. Azathioprine or mercaptopurine [MP] are introduced while the patient is still receiving CsA or tacrolimus, and steroids are being tapered. The justification for thiopurines in this setting, even in patients who are 5-ASA naive, is the high colectomy rate [36–69% in the 12 months following introduction of CsA[119,120,281,282]]. Retrospective series have suggested that thiopurines reduce the risk of colectomy after induction with CsA.[119,120,283]

After IV CsA, a switch to oral therapy occurs as soon as a clinical response has been achieved, with a view to acting as a 'bridge' until the therapeutic effects of thiopurines are achieved.

12.2.3. Anti-TNF and anti-adhesion therapy

ECCO statement 12H

In patients responding to anti-TNF, maintaining remission by continuing anti-TNF therapy with or without thiopurines [EL1] is appropriate. The use of thiopurine maintenance is an alternative option [EL3]

ECCO statement 12I

Anti-TNF or vedolizumab may be used as first-line biological therapy. Vedolizumab is effective in patients failing anti-TNF [EL2]. In patients responding to vedolizumab, maintenance therapy with vedolizumab is appropriate [EL2]

ECCO statement 12J

In thiopurine-naïve patients with severe colitis responding to steroids, ciclosporin or tacrolimus, thiopurines are appropriate to maintain remission [EL2]. Patients responding to infliximab should continue infliximab with or without thiopurines [EL2]; thiopurine maintenance is an alternative option [EL4]

12.2.3.1. Anti-TNF for maintenance of remission

In the ACT studies,[186] a significantly higher proportion of patients had a clinical response or remission with IFX at Weeks 8 and 30 [and at Week 54 in the ACT 1 trial], compared with placebo. In ACT 1, remission rates at Week 54 were 35% [5 mg/kg], 34% [10 mg/kg], and 17% [placebo]. In ACT 2, remission rates at Week 30 were 26% [5 mg/kg], 36% [10 mg/kg], and 11% [placebo]. The proportion of patients with a sustained clinical remission at all time points was 7% [placebo] and 20% [5 mg/kg] after 54 weeks in ACT 1, and 2% [placebo] and 15% [5 mg/kg] after 30 weeks in ACT 2. The steroid-free remission rates in the 74 patients receiving corticosteroids at baseline were very modest, although still statistically significant. In ACT 1, steroid-free remission at Week 54 was achieved in 24% [5 mg/kg], 19% [10 mg/kg], and 10% [placebo]. In ACT 2, the corresponding values at Week 30 [7 months] were 18%, 27%, and 3%. The rates of clinical response and remission were similar between the subpopulations of patients who were 'corticosteroid-refractory' [i.e. those receiving corticosteroids at baseline] and those who were 'not corticosteroid-refractory'.

In long-term follow-up, 121 outpatients with refractory UC treated with IFX were analysed for colectomy-free survival. Secondary measures were sustained clinical response and serious adverse events. From the 81 patients [67%] with an initial clinical response to IFX, 68% had a sustained clinical response. No independent predictors of sustained clinical response could be identified. Over a median [interquartile range] [IQR] follow-up period of 33.0 [17.0–49.8] months, 21 patients [17%] came to colectomy. Independent predictors of colectomy were absence of short-term clinical response [hazard ratio 10.8, 95% CI 3.5–32.8; $p < 0.001$], a baseline CRP level ≥ 5 mg/l [HR 14.5, 95% CI 2.0–108.6; $p = 0.006$], and previous IV treatment with corticosteroids and/or CsA [HR 2.4, 95% CI 1.1–5.9; $p = 0.033$].[284] Complete mucosal healing has independently been shown to be associated with a lower colectomy rate [95% colectomy-free at Week 54, compared with 80% with an endoscopic Mayo Clinic sub-score of 3; $p = 0.0004$].[224]

In ULTRA 2, significantly more adalimumab-treated than placebo-treated patients achieved clinical remission at Week 8 [16.5% vs 9.3%; $p = 0.019$], Week 52 [17.3% vs 8.5%; $p = 0.004$], and both Weeks 8 and 52 [8.5% vs 4.1%; $p = 0.047$]. Similar significant results were observed at all time points for clinical response and mucosal healing. As already discussed [section 11.3.1], in contrast to the ACT and PURSUIT studies, patients were allowed previous anti-TNF therapy [this group comprised 40% of the final study population]. Importantly, treatment benefits were greatest in anti-TNF naïve patients, since among patients who had previously received anti-TNF, rates of remission at Week 8 were no better than placebo and rates at Week 52 were just 10.2% [vs placebo 3%, $p = 0.039$]. This study remains the only RCT to test the efficacy of alternative anti-TNF therapy in previous treatment failures. Nonetheless, reported rates of maintenance of remission at 1 year, in case series following switching IFX treatment failures to adalimumab in UC, range from 10% to 50%.[192]

The risk of all-cause [0.18 vs 0.26; $p = 0.03$], UC-related [0.12 vs 0.22; $p = 0.02$], and UC- or drug-related [0.14 vs 0.24; $p = 0.005$] hospitalisations by Week 52 were significantly lower in patients receiving adalimumab in comparison with placebo in the combined patient cohort of the ULTRA 1 and 2 trials.[285] Fou-year follow-up data from ULTRA 1 and 2, along with the long-term extension study ULTRA 3, have been reported.[286] For the 199 patients followed to Week 208, the remission rate was 24.7%.

The efficacy of subcutaneous golimumab for maintenance of remission in moderate to severe UC was evaluated in the PURSUIT-M trial.[189] Anti-TNF naïve patients who responded in the induction studies [$n = 464$] were re-randomised to placebo or injections of

50 mg or 100 mg golimumab every 4 weeks through Week 52. Among the subset of patients who had achieved a response by Week 6 in the induction studies, clinical response was maintained through Week 54 in 47.0% of patients receiving 50 mg golimumab, 49.7% of patients receiving 100 mg golimumab, and 31.2% of patients receiving placebo [$p = 0.010$ and $p < 0.001$, respectively]. At Weeks 30 and 54, a higher percentage of patients who received 100 mg golimumab were in clinical remission and had mucosal healing [27.8% and 42.4%, respectively,] than patients given placebo [15.6% and 26.6%; $p = 0.004$ and $p = 0.002$, respectively].[189] Sustained clinical benefit up to 2 years has been published.[287]

12.2.3.2. Therapeutic drug monitoring

A dose-response relationship has been reported for all anti-TNF agents between serum drug levels and clinical outcomes.[186,190,288] Therapeutic drug monitoring is being increasingly adopted to try to optimise outcomes, particularly during maintenance treatment.[289,290] The TAXIT trial randomised 263 adults with IBD [85 with UC] to drug level-based optimisation of IFX dosing during maintenance treatment or to dose titration based upon clinical judgement. Clinical remission did not differ between the two groups, but significantly fewer relapses were observed in the concentration-based dosing arm over 1 year; pharmaco-economic evaluation showed small overall cost savings using concentration-based dosing.[291] A retrospective review of 247 patients [42 with UC] suggested that trough levels or anti-drug antibodies to IFX or adalimumab guide therapeutic decisions in more than two-thirds of patients.[292] A recent meta-analysis of 13 studies on the use of anti-drug antibodies and IFX trough levels indicated that the presence of anti-drug antibodies was associated with more loss of clinical response in IBD patients, although this was not significant in UC patients.[293]

12.2.3.3. Combining anti-TNF and immunomodulators

As discussed above [sections 11.3.1 and 11.3.3], the superior efficacy of IFX in combination with azathioprine has been demonstrated in the UC-SUCCESS study for biologic- and IM-naïve patients with steroid-refractory disease.[191] Although similar data are lacking for patients refractory to IM therapy, as with CD,[294] the combination of IFX and a thiopurine analogue is probably justified to decrease immunogenicity, which is the source of infusion reactions and loss of response.[206,207,295] In a retrospective Italian study, combination therapy of IFX with thiopurines was an independent predictor for sustained clinical response [$p < 0.0001$; hazard ratio 3.98, 95% CI 1.73–9.14].[148] It is not known whether subsequent IM discontinuation is deleterious in UC, although indirect evidence in CD from a single centre, open-label, randomised withdrawal trial showed that IMs can be stopped after 6 months with no loss of response to IFX over 2 years.[296]

Although RCT data are currently lacking, neither subgroup analysis of clinical trials, nor retrospective analysis of pharmacokinetic samples, would appear to support a similar conclusion regarding IM co-prescription for adalimumab or golimumab.[189,208]

12.2.3.4. Vedolizumab for maintenance of remission

The efficacy of vedolizumab for maintenance of clinical remission in patients responding to induction therapy was evaluated in the GEMINI 1 study.[193] At Week 52, 41.8% of initial responders who continued to receive vedolizumab every 8 weeks and 44.8% of patients who continued to receive vedolizumab every 4 weeks were in clinical remission [Mayo Clinic score ≤ 2 and no sub-score > 1], as compared with 15.9% of patients who switched to placebo [$p < 0.001$ for both groups vs placebo]. Rates of durable clinical response [defined as response at both Weeks 6 and 52], durable clinical remission [remission at both Weeks 6 and 52], mucosal healing, and glucocorticoid-free remission, were all significantly higher among patients assigned to vedolizumab. No clear differences in efficacy were observed between the two vedolizumab regimens, although treatment intensification to 4-weekly dosing has been reported to recapture clinical response in patients losing response to 8-weekly dosing.[297] Concurrent treatment with glucocorticoids or IMs did not substantively affect the efficacy of vedolizumab and, importantly, the benefit over placebo appeared to be consistent regardless of previous anti-TNF failure.[298] The frequency of adverse events was similar in the vedolizumab and placebo groups. A long-term, open-label extension of the GEMINI-1 study has shown sustained benefit to 3 years for a significant number of initial responders.[297] As for anti-TNF agents, vedolizumab shows a dose-response relationship to clinical outcomes,[299] providing interest in dose-adjustment based upon drug-level testing.

Currently, there is no reliable evidence to guide the choice of biologic agent for maintenance treatment in UC. No head-to head, prospective trials are available. In a recent network meta-analysis, IFX, adalimumab, golimumab, and vedolizumab were all superior to placebo for maintenance of remission and response; however, superiority of one agent over another could not be clearly established[221] and further studies are needed.

12.2.4. Probiotics

Three RCTs have compared *E.coli* Nissle [EcN] to 5-ASA for maintenance of remission in UC. In a multicentre, double-blind study, 120 outpatients received 1.5 g/day 5-ASA or 100 mg/day EcN [corresponding to 25 x 10^9 viable *E. coli* bacteria] for 4 days, and then 200 mg/day.[300] Concomitant medications were not permitted. After 12 weeks, 11% of patients receiving 5-ASA and 16% of those receiving the probiotic relapsed. Subsequently 116 patients with active UC were randomised to receive either 5-ASA 2.4 g/day, reducing to 1.2 g/day after remission, or 200 mg/day of EcN.[301] All patients also received an initial 7-day course of oral gentamicin and either rectal or oral steroids in variable doses. The remission rate was 75% in the corticosteroid plus 5-ASA group, and 68% in the corticosteroid plus EcN group [p = ns]. During 1-year follow-up, relapse occurred in 73% of the 5-ASA group and 67% of the EcN group [p = ns], after weaning off steroids. Finally, an equivalence study was conducted in 327 patients with UC in remission for no longer than 12 months, who were treated with either 5-ASA 1.5 g/day or EcN for 1 year.[302] The relapse rate was 45% in the EcN group *vs* 36% in the 5-ASA group [p = ns]. It was concluded that EcN is not inferior to the established standard 5-ASA for maintenance of remission in UC.

In addition to these RCTs, an open-label pilot study investigated the clinical benefit of EcN for maintenance therapy in young patients with UC. A total of 34 patients with UC in remission, aged between 11 and 18 years, were allocated either to EcN [two capsules daily, $n = 24$] or 5-ASA [median 1.5 g/day, $n = 10$], observed over 1 year. This small study was underpowered to show any difference or equivalence, but the relapse rate was 6/24 in the EcN group and 3/10 in the 5-ASA group. Data on the patients' global health and development were favourable and no serious adverse events were reported.[303] The utility of EcN is limited by its limited availability.

No evidence has yet been reported that any other probiotic is effective for maintaining remission in patients with UC;[304–306] see Supplementary material for details (available at *ECCO-JCC* online).

12.2.5. Other treatments

12.2.5.1. Antibiotics

Ciprofloxacin [1–1.5 g/day] or placebo was administered for 6 months to 83 patients referred with active UC refractory to conventional treatment, in an RCT. All the patients were initially treated with high but decreasing doses of prednisone, and 5-ASA. The treatment failure rate was 21% in the ciprofloxacin-treated group and 44% in the placebo group [p = 0.02]. However the study design can be criticised, including the inclusion criteria, lack of standardised definition of response, confounding effects of concomitant therapies, suboptimal baseline treatment, and unbalancing between groups.[307] Consequently, ciprofloxacin should not be considered effective for maintaining remission in UC until further trials are supportive. In another double-blind, randomised trial, metronidazole [0.6 g/day] and sulphasalazine [2 g/day] were compared for maintenance of remission in 40 patients with UC in remission for less than 12 months.[308] After 1 year, metronidazole was found to be slightly more effective than sulphasalazine. These data were regarded as insufficient by the Consensus to recommend antibiotics for maintenance of remission in UC.

12.2.5.2. Methotrexate

Data on MTX for maintenance of remission in UC are few. The single placebo-controlled RCT was principally designed for induction of remission in refractory, active UC and used an oral dose of 12.5 mg/week, which is probably sub-therapeutic.[309] The proportion of patients who relapsed after first remission [MTX 64% vs placebo 44%] or who maintained remission at 9 months [MTX 36% vs placebo 54%] were not significantly different. An open-label study compared MP, MTX, and 5-ASA in 72 steroid-dependent IBD patients, including 34 with UC.[271] Patients were randomly assigned in a 2:2:1 ratio to receive MP 1 mg/kg, MTX 15 mg/week orally, or 5-ASA 3g/day. All patients who achieved remission at Week 30 were then included in a maintenance study for 76 weeks. A significantly higher proportion of patients achieved remission in the MP group [79%] than in the 5-ASA group [25%], with no statistical differences compared with the MTX group [58%]. For maintenance of remission, the highest rate was found in the MP group [64%] compared with MTX [14%] and 5-ASA [0%].

Several retrospective series have been published.[310,311] Most of the patients included had failed or were intolerant of azathioprine and were treated with MTX at various doses and routes of administration. The response or remission rates ranged from 30% to 80%, when the drug was given by parenteral route in doses between 20 mg and 25 mg, suggesting that some patients with UC may respond to MTX. MTX [median oral dose 20 mg/week] was tolerated by 27/31 [87%] patients who had been unable to tolerate azathioprine. Of those treated with MTX after failure with azathioprine, 5/11 patients had a colectomy, compared with 5/31 patients intolerant of azathioprine.[311] In another study, MTX induced a response in 65% [15/23] of those who were either previously intolerant and in 78% [7/9] of those who had previously failed thiopurine therapy.[310] The results are heterogeneous and it is possible that the dose of MTX is a determinant of efficacy, but the Consensus considered that there is currently insufficient evidence to recommend MTX for maintenance of remission in UC. A Cochrane systematic review reached the same conclusion.[312]

12.3. Duration of maintenance therapy

ECCO statement 12K

Mesalamine maintenance treatment should be continued long-term [EL3]; this may reduce the risk of colon cancer [EL3]

12.3.1. Aminosalicylates

Studies have been published to assess whether sulphasalazine is effective at preventing relapse in patients with UC after a long duration of remission. In one study, the authors found no statistical benefit for patients who had been symptom-free on sulphasalazine for more than a year.[313] However, the number of patients was small, the duration of follow-up only 6 months, and patients were selected using clinical symptoms without endoscopic or histological criteria. In another study, sigmoidoscopy and rectal biopsy were used at entry.[244] The authors found that maintenance treatment with sulphasalazine 2g/day reduced relapse rates, even in the subgroup of patients who had been on sulphasalazine for more than 3 years. A double-blind withdrawal RCT 26 years later included 112 patients with UC in clinical, endoscopic and histological remission, who had been on sulphasalazine or 5-ASA for at least 1 year.[314] Patients were randomised to oral 5-ASA 1.2 g/day or placebo for 1 year. Despite the small numbers, patients were stratified according to the duration of disease remission preceding randomisation. In patients with disease remission for 1–2 years, 5-ASA appeared more effective than placebo for preventing relapse at 12 months [5-ASA 23% and placebo 49%; p = 0.035]. For patients who had been in remission for more than 2 years however, no statistically significant difference was observed between relapse rates [5/28 vs 6/23, or 18% vs 26%, respectively], but patient numbers were very small. The results of this study should be regarded with caution, not only because of the low power, but also because the maintenance dose was lower than that now recommended [see section 12.2.1].

ECCO statement 12L

In view of limited evidence, no recommendation can be given for the duration of treatment with azathioprine, anti-TNF, or vedolizumab, although prolonged use of these medications may be needed [EL4]

12.3.2. Thiopurines

There are few data on factors predicting response to azathioprine, and there is uncertainty regarding the optimal duration of treatment. In a retrospective analysis with 622 patients with either CD or UC, the remission rates at 6 months were 64% and 87%, respectively. The proportion of patients thereafter remaining in remission at 1, 3, and 5 years was 0.95, 0.69, and 0.55, respectively. There was no difference in relapse rates between CD and UC. After stopping azathioprine, the proportion of patients remaining in remission at 1, 3, and 5 years was 0.63, 0.44, and 0.35 [of 222 patients] respectively. The duration of azathioprine treatment did not affect the relapse rate after stopping treatment [p = 0.68].[279] A recent systematic review supports continuing maintenance thiopurines in patients in remission.[315]

12.3.3. Anti-TNF and vedolizumab therapy

Several studies, most of them neither prospective nor randomised, have reported long-term efficacy data in UC [reviewed in[316]]. Extension studies of clinical trials support sustained benefit for initial responders to

IFX, adalimumab, golimumab, and vedolizumab, but the interpretation of results is complicated by differences in trial design and thus direct comparisons between studies are not possible.[286,287,297,317] No withdrawal study of anti-TNF therapy has been reported in UC, although a multinational, retrospective cohort study reported an association between IFX discontinuation and increased risk of relapse; following IFX re-initiation, response was attained in 77% and remission in 51%.[318] This has been addressed recently by systematic review[319] reporting that 28% of UC patients relapse at 12 months after anti-TNF withdrawal.

12.4. Maintenance of remission and transition from paediatric to adult care

ECCO statement 12M

Transition to adult services should be coordinated by paediatric and adult teams. It usually commences in mid adolescence, depending on the development of the patient and the availability of paediatric and adult gastroenterologists [EL5]

ECCO statement 12N

Transition is successful when the patient has acquired the self-management skills to visit and talk to the doctor alone, understands disease management including risks and benefits, and is adherent to treatment [EL4]

The optimal timing of transition from paediatric to adult management of UC has to be decided on an individual basis by a joint team of paediatric and adult gastroenterologists. The transition period usually starts from the age of 16–18 years, depending on patient development and availability of qualified paediatric and adult gastroenterologists. This area has been addressed by an ECCO Topical Review.[320]

Conflict of Interest

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 statement is not only stored at the ECCO Office and the editorial office of *JCC*, but is 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 authors.

Disclaimer

The ECCO Consensus Guidelines are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO Consensus Guidelines. The European Crohn´s and Colitis Organisation and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO Consensus Guidelines.

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