Review

Digestion

Digestion
DOI: 10.1159/000504092

Received: May 21, 2019
Accepted: October 13, 2019
Published online: January 16, 2020

Treatment Algorithm for Mild and Moderate-to-Severe Ulcerative Colitis: An Update

Emanuel Burri[a] Michel H. Maillard[b] Alain M. Schoepfer[c] Frank Seibold[d] Gert Van Assche[e] Pauline Rivière[f] David Laharie[f] Michael Manz[g]

[a]Department of Gastroenterology and Hepatology, Cantonal Hospital Baselland, Liestal, Switzerland; [b]Crohn and Colitis Center, Gastroentérologie Beaulieu SA, Lausanne, Switzerland; [c]Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; [d]Crohn-Colitis Zentrum, Hochhaus Lindenhofspital, Bern, Switzerland; [e]Department of Gastroenterology, University of Leuven and University Hospitals Leuven, Leuven, Belgium; [f]Hépato-gastro-entérologie, Centre Hospitalier Universitaire, Bordeaux, France; [g]Department of Gastroenterology and Hepatology, Clarunis, Basel, Switzerland

Keywords
Ulcerative colitis · Moderate to severe · Acute · Treatment

Abstract
Background: Patient care in ulcerative colitis (UC) remains challenging despite an array of established treatment options and emerging new therapies. The management of UC therapy should be guided by the endoscopic extent of inflammation, disease severity, and prognostic factors of poor outcome. Complete remission, defined as durable symptomatic and endoscopic remission without corticosteroid therapy, is the desired treatment goal. ***Summary:*** This review focuses on treatment recommendations for different clinical scenarios in moderate-to-severe UC: Active UC of any extent not responding to aminosalicylates, steroid-dependent UC, steroid-refractory UC, immunomodulator-refractory UC, and acute severe UC. Comprehensive treatment algorithms for daily clinical practice were developed based on published guidelines and current literature. ***Key Messages:*** While current treatment options including a number of biologicals and small molecules have evolved UC treatment to achieve sustained remission in a majority of patients, upcoming treatment options with different molecular pathways and different modes of actions will further increase the need for personalized medicine. © 2020 S. Karger AG, Basel

Introduction

Ulcerative colitis (UC) is characterized by a chronic immune-mediated inflammation of the colon. The cause of the aberrant immune response remains largely unknown, but dietary and environmental risk factors have a role as well as host factors such as genetic susceptibility and gut microbiota [1]. The annual incidence is higher in industrialized countries and has steadily increased over the last decades worldwide [2].

Clinical presentation of UC is characterized by a gradual or sudden onset of hematochezia, diarrhea, and abdominal pain [3]. Symptoms may also include urgency and fecal incontinence, while weight loss and fever are typical features of severe disease activity. The presence of

KARGER

© 2020 S. Karger AG, Basel

E-Mail karger@karger.com
www.karger.com/dig

Emanuel Burri, MD
Department of Gastroenterology and Hepatology
Cantonal Hospital Baselland
Rheinstrasse 26, CH–4410 Liestal (Switzerland)
E-Mail emanuel.burri@ksbl.ch

anemia, hypoalbuminemia, and elevated C-reactive protein (CRP) may suggest inflammatory bowel disease, elevated fecal calprotectin is a sensitive (but not specific) indicator of intestinal inflammation [4]. The diagnosis of UC is based on a combination of clinical, laboratory, imaging, and endoscopic parameters, including histopathology. Endoscopic findings include continuous colonic inflammation characterized by erythema, loss of normal vascular pattern, granularity, erosions, friability, bleeding, and ulcerations [5, 6].

At diagnosis, most patients have left-sided UC (40%) with mild-to-moderate disease activity [7]. The natural course of UC follows a gradual progression of disease extension which is seen in 10–30% of patients. Most patients have a chronic remitting and relapsing disease course with a 10-year cumulative risk of relapse of 70–80% [8, 9]. The 5- and 10-year cumulative risk of colectomy is 10–15% [10, 11].

Therapeutic management in UC should be guided by the endoscopic extent of inflammation, disease severity, and prognostic factors of poor outcome, for example, age <40 years at diagnosis, extensive disease, or the presence of extraintestinal manifestations and response to previous medication [12–14]. The goal of treatment is complete remission defined as durable symptomatic and endoscopic remission without corticosteroid therapy. Current data do not yet support histologic healing as a treatment goal in UC [15, 16].

Definitions

The extent of UC may vary considerably and is described by the Montreal Classification [17]. The endoscopic extent is categorized as distal to the rectosigmoid junction (E1, proctitis), extending anywhere from the sigmoid to the splenic flexure (E2, left-sided colitis or distal colitis) or extending beyond the splenic flexure (E3, extensive colitis or pancolitis). The extent of inflammation has implications on patient medical management and is also a risk factor for the development of colorectal cancer in case of left sided or extensive disease. Proximal extension of proctitis may occur in 20–50% of adult patients with UC [18]. Disease severity also influences treatment modalities and different clinical indices of UC disease activity have been suggested (Table 1) [19]. Most national and international guidelines recommend classifying UC into mild, moderate, and severe disease activity based on the Truelove and Witts' Severity Index [12, 14, 20, 21]. There is no fully validated definition of remission, but it is suggested to use a combination of clinical parameters (stool frequency ≤3/day with no bleeding) and no mucosal lesions at endoscopy [20].

Active UC of Any Extent Not Responding to Aminosalicylates

In mild-to-moderate UC of any extent, aminosalicylates (5-ASA) such as mesalamine are the preferred initial treatment [12–14] (Fig. 1). In patients with disease activity limited to the rectum, topical therapy alone might suffice, but combination therapy is more effective and is also recommended for left-sided and extensive UC [22, 23]. Table 2 gives an overview on current treatment options.

Except in case of isolated proctitis, where topical corticosteroids alone may be considered, treatment with oral corticosteroids should be initiated in patients who do not respond adequately to 5-ASA [13]. In case of isolated proctitis, topical corticosteroids alone might be considered. The introduction of corticosteroids should be a shared decision-making process that includes patient's preference of therapy and tolerance to 5-ASA. It is, however, recommended to start corticosteroids in patients with sustained rectal bleeding for 2 weeks, persistent abdominal symptoms after 6 weeks of adequate therapy with 5-ASA or if symptoms deteriorate [13]. In selected cases, a prolonged therapy with up to 16 weeks might still be able to achieve remission.

Both conventional oral corticosteroids and budesonide have shown to be superior to placebo and 5-ASA in inducing remission in active UC [24–26]. Budesonide is a second-generation corticosteroid with an ileo-colonic release mechanism and low systemic bioavailability. Recently, a new formulation of budesonide multimatrix (MMX) with a colonic delivery technology to permit the release of budesonide at a controlled rate throughout the colon has been introduced. Budesonide-MMX is recommended in patients with left sided or extensive UC with mild-to-moderate disease activity who are intolerant or refractory to 5-ASA [13, 27]. It improved clinical and endoscopic parameters more likely than placebo but direct comparison in efficacy against conventional corticosteroids are lacking [28, 29]. Also, budesonide-MMX seems to be more efficacious in left-sided colitis, and oral non-MMX budesonide is not superior to placebo in the treatment of UC [30]. However, topical non-MMX budesonide is effective in inducing remission in UC confined to the rectum [31, 32]. As almost 50% of UC patients experience corticosteroid-related adverse events

Table 1. Clinical and endoscopic scores adapted from [19]

Name	Abbreviation	Range (remisson)	Parameters	Strength	Weakness
Clinical scores					
Simple Colitis Clinical Activity Index	SCCAI	0–19 (≤2)	Bowel frequency (day) Bowel frequency (night) Urgency of defecation General well being Extracolonic features	Pure patient-questionnaire Simple, easy to handle, reliable	Not validated
Partial Mayo Scoring Index	PMS	0–9 (≤1)	Stool frequency Rectal bleeding Physician's global assessment	Most widely used score Discriminates active disease from remission	Not validated Includes doctor's subjective assessment
Truelove and Witts Severity Index	TWSI	Mild moderate severe	Bowel movements Blood in stools Pyrexia Anemia ESR	Objective criteria for acute severe colitis Useful for prognosis	Not validated (but widely used)
Endoscopic scores					
Ulcerative Colitis Endoscopic Index of Severity	UCEIS	0–8 (≤1)	Scoring (points) of vascular pattern, bleeding, erosions and ulcers of the worst affected area	Validated Simple to use Good reproducibility	No validated definition of mucosal healing or response to treatment Does not reflect disease-extension No gradation of mild, moderate, and severe disease
Endoscopic Mayo Score (Mayo endoscopic subscore)	MES	0–3 (≤1)	Staging based only on endoscopic exploration of erythema, vascular pattern, friability, erosions, ulcerations spontaneous bleeding	Simple to use widespread in clinical studies and clinical practice	Overlapping and subjective scoring lead to reduced reproducibility No validated definition of mucosal healing or response to treatment Not reflects disease-extent

(acne, sleep- and mood disturbance, glucose intolerance, and dyspepsia), budesonide-MMX with its low systemic bioavailability should always be considered as first-line therapy in patients not responding to 5-aminosalicylates (5-ASA).

In patients not responding to budesonide-MMX or with moderate-to-severe UC disease activity, conventional oral corticosteroid therapy (0.75–1 mg/kg oral prednisone-equivalent, not >60 mg/day) should be considered [33, 34]. After 2 weeks, patients should be assessed, and the daily dosage lowered by 5–10 mg every week in case of clinical response. A course of 8 weeks therapy is appropriate as to prevent early relapse.

In patients not responding adequately to conventional oral corticosteroids, stool should be retested for bacteria, parasites, and Clostridium difficile toxin as well as sigmoidoscopy with biopsies to rule out cytomegalovirus (CMV) should be performed [35]. If infectious disease is excluded a course of intravenous corticosteroids may be initiated and if unsuccessful, the patient is considered to have steroid-refractory UC (see the corresponding section below). If a patient fails to taper corticosteroids below the equivalent of prednisolone 10 mg/day within 3 months or relapses within 3 months, he is considered steroid dependent (see the corresponding section below). In patients having successfully tapered corticosteroids, an attempt should be made to reestablish maintenance therapy with topic and/or oral 5-ASA [36, 37]. In case of relapse, combination therapy with corticosteroids and azathioprine (AZA)/6-mercaptopurine (6-MP) or biologic therapy should be considered [38–41].

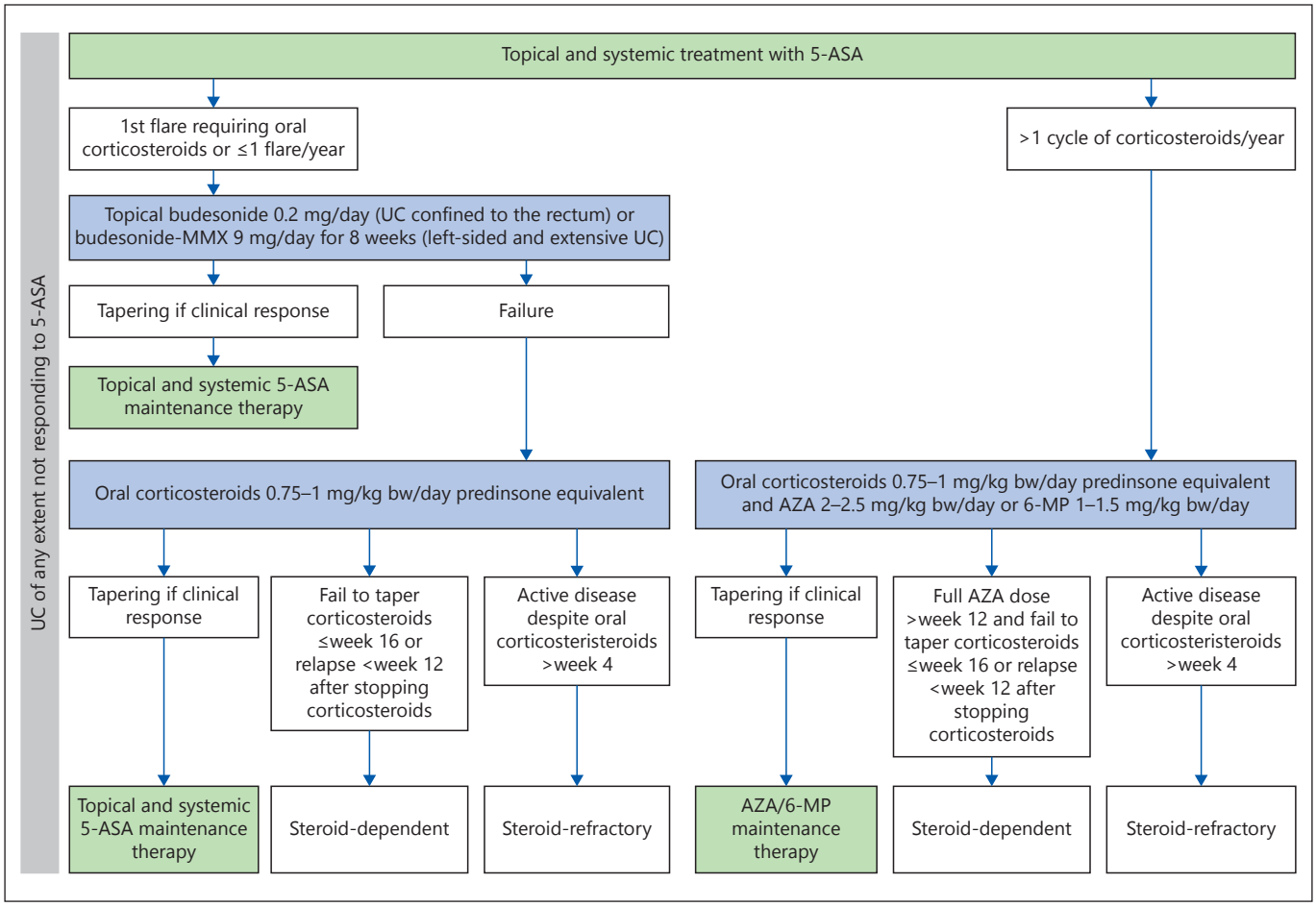

Fig. 1. Active ulcerative colitis (UC) of any extent not responding to 5-aminosalicylates (5-ASA). MMX, multimatrix; AZA, azathioprine; 6-MP, 6-mercaptopurine.

Alternative strategies to control UC not responding to 5-ASA include VSL#3 [42], phosphatidylcholin [43], and fecal transplantation [44, 45], but data on efficacy are limited and cannot be recommended outside of clinical studies.

Steroid-Dependent UC

Steroid-dependent UC defines a disease course that initially responds to oral corticosteroids but fails to taper below the equivalent of prednisolone 10 mg/day within 3 months or that relapses within 3 months after steroid discontinuation [46] (Fig. 2). Corticosteroid use in UC is associated with higher risk for relapse and colectomy [47]. Given the adverse short- and long-term effects of corticosteroids, to achieve and maintain a corticosteroid-free remission remains paramount. After initial exposure to corticosteroids around two-third will require reintroduction of corticosteroids, and one-third will become steroid-dependent over time [48]. Patients undergoing oral corticosteroid induction therapy should therefore be clinically assessed within 2 weeks in order to identify non-responders early and to avoid delayed therapy escalation [13]. In case of partial response, induction therapy with full-dose corticosteroids may be extended for another 2 weeks in selected patients, but if no clinical response is seen, therapy should be modified.

Prior to therapy escalation, diagnostic work-up should include stool test for infectious colitis and sigmoidoscopy to rule out CMV. Also, adherence to 5-ASA medication is a factor of relapsing disease activity and has to be discussed with the patient. The prevalence of nonadherence to medication is generally high (40–50%) and may increase to 68% in patients on >4 prescription medications [49, 50]. Other predictors of low adher-

Table 2. Medical therapy for UC

	Substance	Dosage
5-ASA	Mesalazine	2–4.8 g/day (oral) 1–2 g/day (rectal)
Corticosteroids	Budesonide	0.2 mg/day (rectal)
	Budesonide MMX	9 mg/day (oral)
	Prednisone	0.75–1 mg/kg bw/day
	Hydrocortisone	100 mg IV 4 times/day
	Methylprednisolone	125 mg IV/day
Immunosuppressives	AZA	2–2.5 (max. 3) mg/kg bw/day
	6-MP	1–1.5 mg/kg bw/day
	Cyclosporine	2 mg/kg bw/day IV
	Tacrolimus	0.1 mg/kg bw/day Serum concentration 10–15 ng/mL
Biologics	Adalimumab	Subcutaneous Week 0: 160 mg Week 2: 80 mg Week 4: 40 mg Then every 2 weeks: 40 mg Dose escalation: 40 mg weekly
	Golimumab	Subcutaneous Week 0: 200 mg Week 2: 100 mg Week 4: 50 mg Then every 4 weeks: 50 mg (100 mg if patient >80 kg bw)
	Infliximab	Infusion over 30–90 min Week 0: 5 mg/kg Week 2: 5 mg/kg Week 6: 5 mg/kg Then every 8 weeks: 5 mg/kg Dose escalation: every 4 weeks 5–10 mg/kg bw
	Vedolizumab	Infusion over 30 min Week 0: 300 mg Week 2: 300 mg Week 6: 300 mg Then every 8 weeks: 300 mg Dose escalation: every 4 weeks 300 mg
Janus kinase inhibitor	Tofacitinib	Oral tablet 5 or 10 mg First 8 weeks: 10 mg twice daily 10 mg twice daily for another 8 weeks in partial response Thereafter: 5 mg twice daily

5-ASA, 5-aminosalicylates; UC, ulcerative colitis; MMX, multimatrix; bw, body weight; AZA, azathioprine; 6-MP, 6-mercaptopurine.

ence are age <40 years, alcohol consumption, and current smoking habits [51]. Patients with once daily 5-ASA medication have higher remission rates than t.i.d. (86 vs. 73%, $p = 0.03$), and strategies to optimize therapy adherence should include simple dosing options [52].

Patients with steroid-dependent disease should be treated with an either AZA/6-MP, a tumor necrosis factor (TNF)-inhibitor (preferably combined with AZA/6-MP), or vedolizumab. The role of methotrexate within UC treatment algorithms is controversial. ECCO still lists methotrexate as therapeutic option [33], whereas others

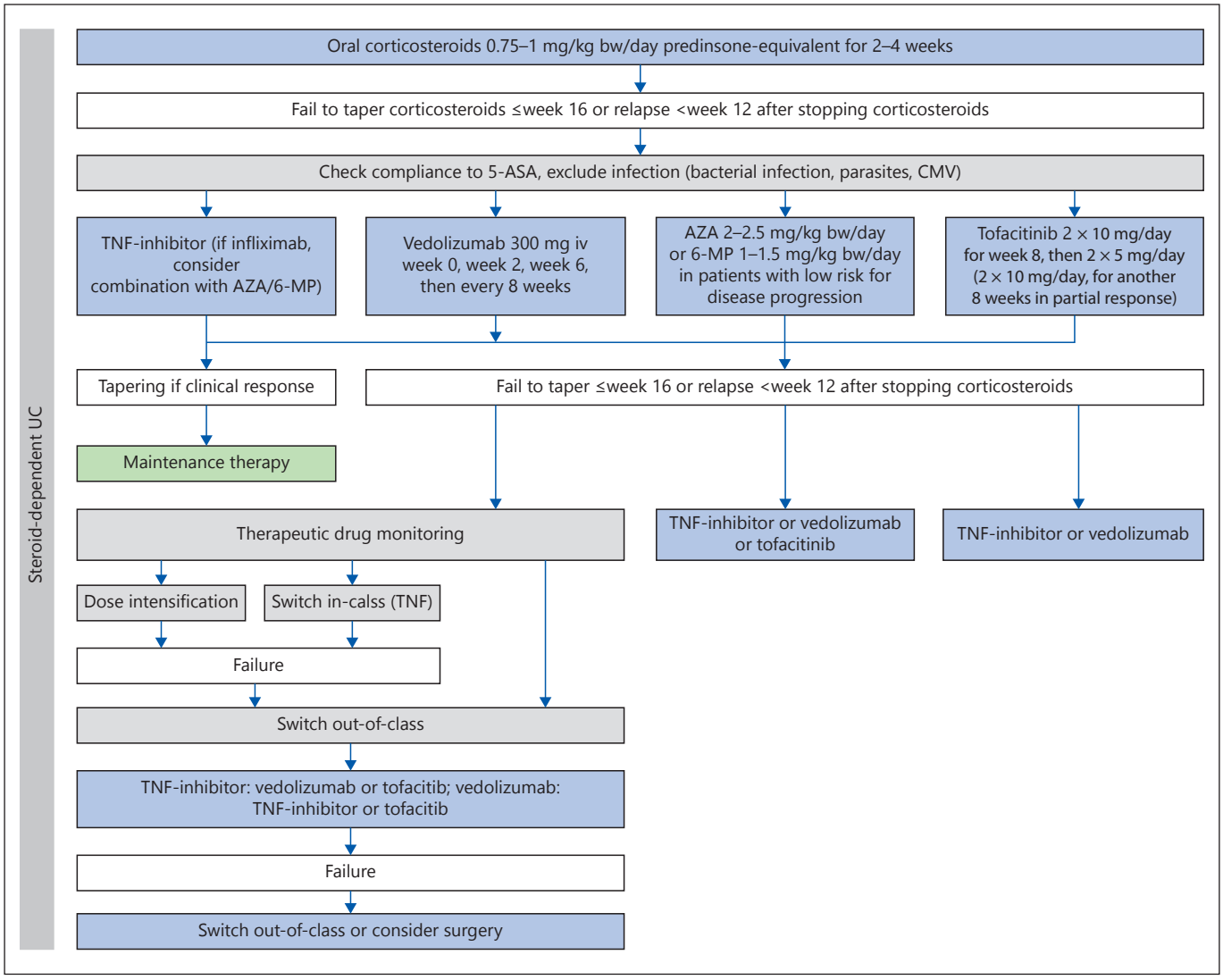

Fig. 2. Steroid-dependent ulcerative colitis (UC). 5-ASA, 5-aminosalicylates; TNF, tumor necrosis factor; AZA, azathioprine; CMV, cytomegalovirus; 6-MP, 6-mercaptopurine.

do not [14]. A recent Cochrane Review summarized that there is no evidence supporting the use of methotrexate for maintenance of remission in UC [53] and since then, 2 additional and complementing trials have also suggested a lack of efficacy for methotrexate [54, 55].

Evidence of several studies supports the benefit of AZA for maintenance of remission in patients with UC [52]. AZA has been shown to be more effective than 5-ASA in achieving clinical and endoscopic remission in corticosteroid-dependent UC [56]. However, thiopurine therapy carries an increased risk for lymphoma and nonmelanoma skin cancer as well as bone marrow suppression, pancreatitis, and hepatotoxicity [57–59]. Therefore, long-term treatment with thiopurines should balance the individual patient's response with the risk and efficacy of therapy. Before treatment with AZA/6-MP is initiated, full blood count including lymphocyte numbers must be obtained. Measurement of thiopurine-S-methyltransferase activity may be considered to guide initial dosing of AZA/6-MP and identify patients at risk for severe bone marrow suppression under therapy [60–62]. However, regular WBC counts are mandatory, as bone marrow suppression may still occur irrespective of TMPT activity [63, 64]. Therapeutic drug monitoring is performed with measurement of 6-thioguanin, a thiopurine metabolite, with higher levels increasing the risk for

leucopenia and possibly aplasia. Suggested through levels are 230–450 pmol/8 × 10^8 red blood cells for monotherapy with AZA/6-MP and >125 pmol/8 × 10^8 red blood cells for combination therapy with a TNF-inhibitor [65]. Treatment response should be evaluated as early as 12 weeks when AZA/6-MP therapy is expected to be fully effective [66]. In summary, AZA/6-MP maintenance therapy is best suited for patients with low risk of progression who responded well to a first course of corticosteroid therapy.

In all other patients with a corticosteroid-dependent course of UC, biologic therapy with either an anti-TNF drug, alone or in combination with AZA/6-MP, vedolizumab, or tofacitinib are the preferred choices. Several studies have shown anti-TNF therapy (infliximab, adalimumab, golimumab) to be effective in achieving corticosteroid-free remission (in about 30%) compared to placebo in patients with moderate-to-severe UC [67–70]. When introducing anti-TNF therapy, combination therapy with AZA/6-MP should always be considered. In the UC SUCCESS trial in biologic-naïve patients, corticosteroid-free remission was achieved in 40% with combination therapy, compared to 22% with infliximab alone [71]. Combination therapy with adalimumab or golimumab, also in AZA/6-MP pre-exposed corticosteroid-dependent patients, has not been studied in randomized controlled trials.

Vedolizumab is a humanized monoclonal antibody that binds to α4β7 integrin on gut-homing lymphocytes and therefore inhibiting endothelial cell adhesion and migration into the intestinal wall. It has been shown to be effective to induce and maintain corticosteroid-free remission in both anti-TNF-experienced and anti-TNF-naïve patients as well as patients with prior AZA//6-MP exposure [72]. The efficacy in TNF-naïve patients seems to be higher and is comparable with that of anti-TNF biologics in this population [73]. The gut-selective properties of vedolizumab with fewer systemic side effects might be advantageous for patients requiring long-term biologic therapy.

Another treatment option is Tofacitinib, an oral janus kinase inhibitor that has recently been licensed for the use in moderate-to-severe UC. Tofacitinib has been shown to induce and maintain remission after treatment failure with either oral corticosteroids, AZA, or anti-TNF therapy [74]. Tofacitinib showed a rapid onset of action with significant improvements of symptoms (stool frequency, rectal bleeding) within 3 days [75]. Endoscopic remission was achieved in 17–19% (compared to 4–8% with placebo) after 8 weeks.

Steroid-Refractory UC

Patients not responding to corticosteroid therapy with 0.75–1 mg/kg body weight of oral prednisolone equivalent within 4 weeks or intravenous corticosteroids for at least 1 week are defined to have steroid-refractory UC after infectious complications (coexistent CMV, *C. difficile*-associated disease) have been excluded [13]. Most patients will not require hospital admission for intravenous corticosteroids. In active steroid-refractory UC, anti-TNF therapy, or vedolizumab is the primary choice as both have shown to achieve corticosteroid-free remission in UC patients receiving corticosteroids [67–70, 72]. If anti-TNF therapy is started, combination with AZA/6-MP is a therapeutic option [71]. Similar to steroid-dependent UC, tofacitinib will be an option, especially in patients with treatment failure to immunomodulatory treatment [74]. Alternatively, tacrolimus may be initiated. Tacrolimus has shown short-term efficacy with clinical response rates reported from 38 to 68% depending on targeted through levels [76] but has also been effective in reducing colectomy rate [77]. The clinical efficacy and safety in moderate-to-severe UC are similar to anti-TNF therapy, but regular monitoring for adverse effects, including nephrotoxicity and opportunistic infections, is warranted. In patients who respond to tacrolimus, AZA/6-MP is recommended for long-term maintenance therapy [13], but tacrolimus might still be an option for patients who are intolerant to infliximab or AZA [78].

Immunomodulator-Refractory UC

Patients having active disease or relapse despite the use of AZA (2–2.5 [max. 3] mg/kg bw/day) or 6-MP (1–1.5 mg/kg bw/day) for at least 3 months and optimized dosing regimen according to 6-thioguanin levels are considered to have immunomodulator-refractory UC [13]. Biologic therapy with either an anti-TNF agent or vedolizumab should be considered (Fig. 3). The clinical efficacy of these compounds has been demonstrated in a number of randomized controlled trials, but comparative trials are mostly lacking to guide the choice of a particular treatment regime [67–70]. The efficacy of infliximab has been compared to other anti-TNF agents using network meta-analysis technology and has shown a (nonsignificant) trend for higher remission rates for infliximab [68, 69]. Results from the VARSITY trial have been presented recently [79]. In patients with moderate-to-severe UC, 31.3% (n = 120/383) of patients who received IV vedoli-

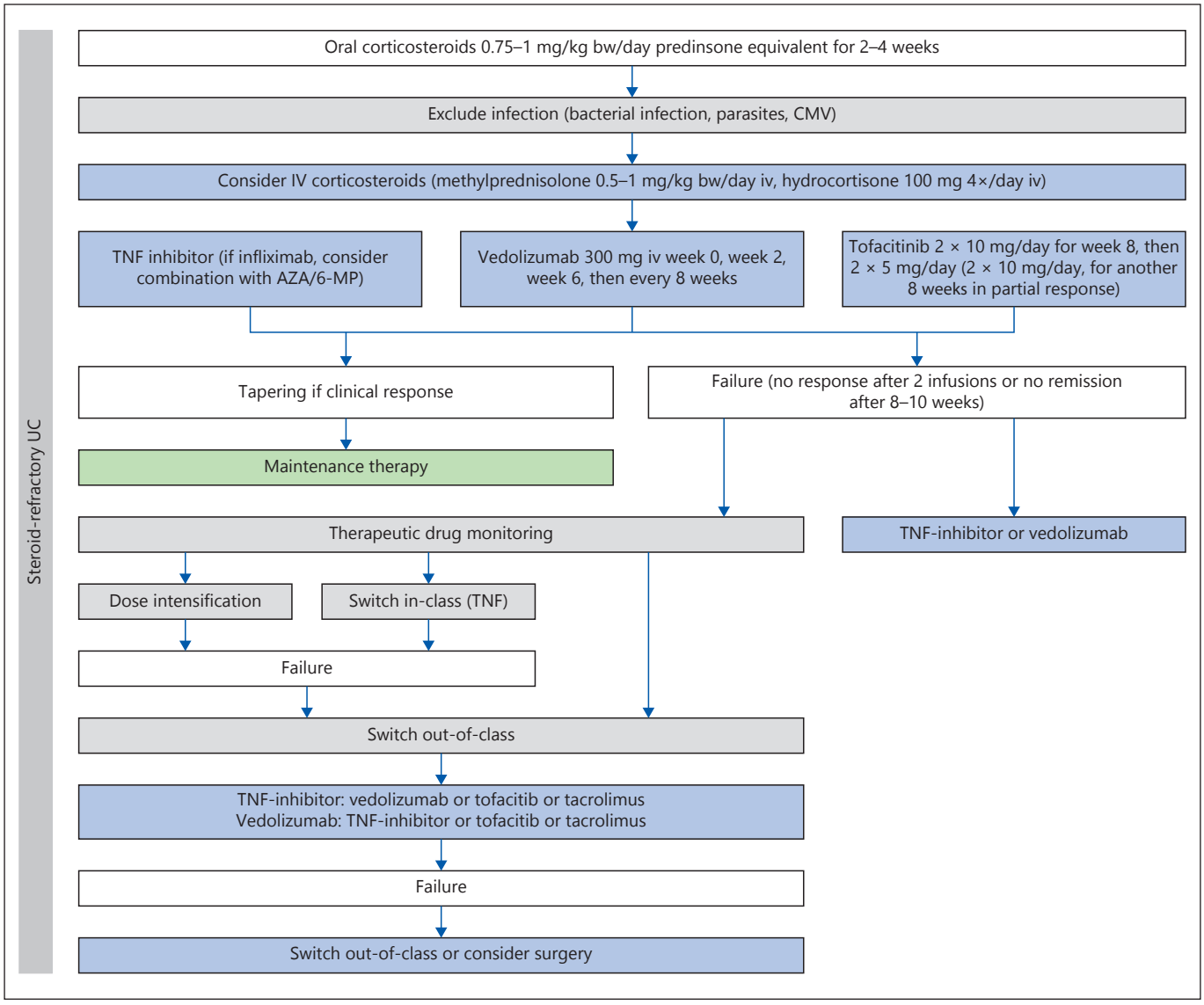

Fig. 3. Steroid-refractory ulcerative colitis (UC). CMV, cytomegalovirus; TNF, tumor necrosis factor; AZA, azathioprine; 6-MP, 6-mercaptopurine.

zumab achieved the trial's primary endpoint of clinical remission, defined as a total Mayo score ≤2 with no subscore >1, at week 52, compared with 22.5% (n = 87/386) of those treated with subcutaneous adalimumab at week 52 (p = 0.0061).

Data on anti-TNFs (mainly infliximab) and AZA/6-MP combination therapy derive from one study that included UC patients that were mostly naïve to AZA/6-MP and from indirect study data [71, 79, 81]. In AZA/6-MP-experienced patients, combination therapy might reduce immunogenicity (e.g., production of antidrug antibodies, increase through levels) and increases treatment efficacy when staring anti-TNF therapy. This might reduce the risk for primary or secondary loss or response. Only limited data are available on combination therapy with vedolizumab and AZA/6-MP. Some evidence points to lower levels of antidrug antibodies with combination therapy, the implications on clinical efficacy and safety remain unclear [82]. Combination therapy with tofacitinib is not recommended as it carries an important risk for opportunistic infections [74].

In case of anti-TNF failure, reinduction, or dose intensification may be an option after careful evaluation including therapeutic drug monitoring with measure-

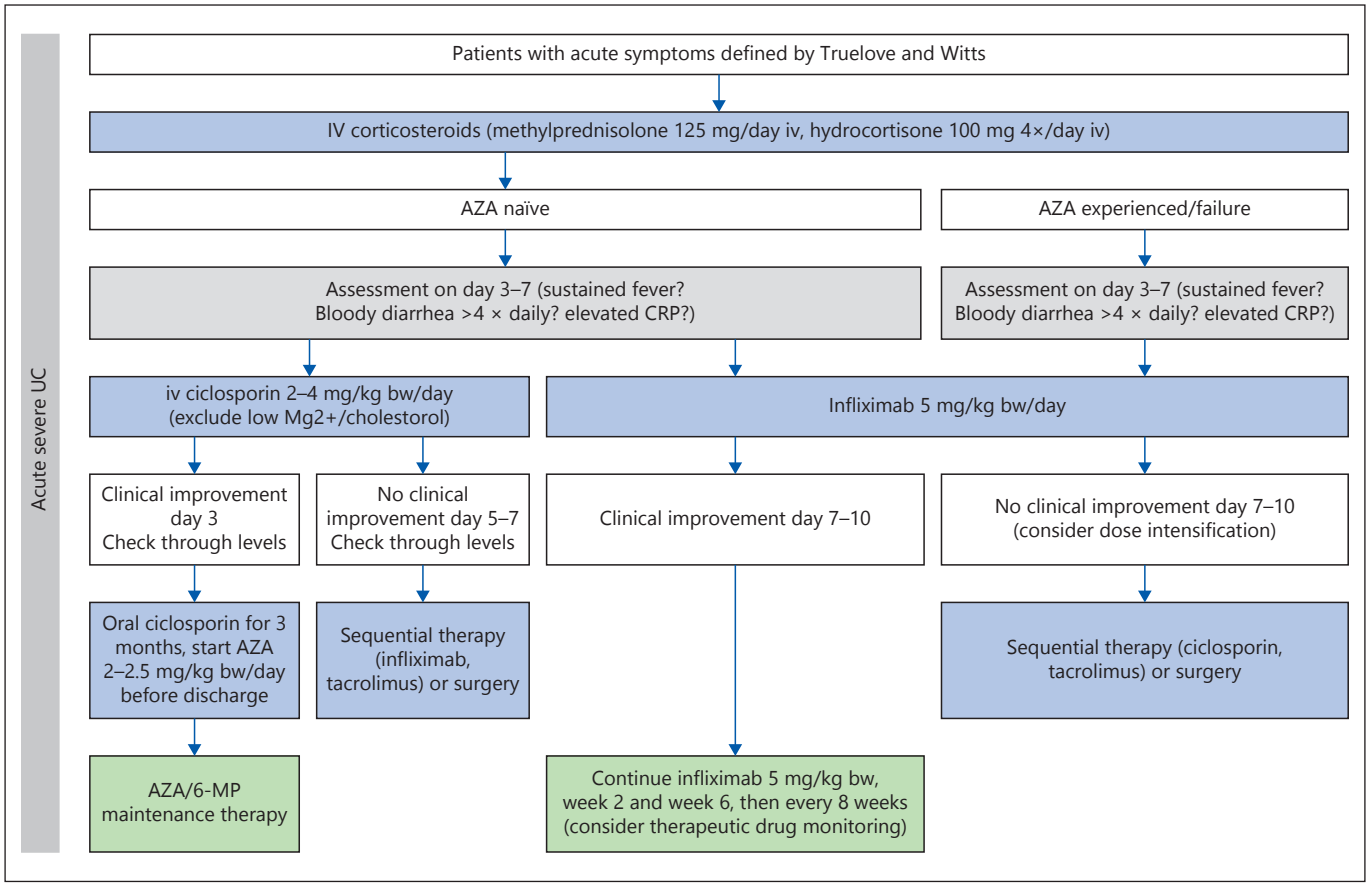

Fig. 4. Acute severe ulcerative colitis (UC). CRP, C-reactive protein; AZA, azathioprine; 6-MP, 6-mercaptopurine.

ment of through levels and antidrug antibodies. Switching to a different anti-TNF therapy is indicated in patients with positive antidrug antibodies, whereas switching to vedolizumab is the preferred choice in case of primary (and secondary) failure [12–14]. Data on anti-TNF therapy after primary failure of vedolizumab are currently not available, but therapy with an anti-TNF drug should still be initiated in this clinical scenario. Again, tofacitinib might be a suitable alternative.

Acute Severe UC

Approximately 20% of patients with UC experience at least one severe exacerbation during the course of their disease. Acute severe UC is diagnosed according to Truelove and Witts' criteria (Table 1) [21]. The definition is based on ≥6 blood stained stools daily, with 1 or more of the 4 additional criteria: hemoglobin <105 g/L, ESR >30 mm/h or CRP >30 mg/L, fever >37.8 °C, and tachycardia >90 b/min. These patients must be admitted to a hospital, preferably one that provides specialized surgical backup, in case a colectomy is warranted [12–14]. Acute severe UC carries a significant morbidity and mortality (1%) [83].

Intravenous corticosteroids with either methylprednisolone or hydrocortisone remain first-line treatment and approximately 65% will respond [84] (Fig. 4). In responding patients, the choice of long-term treatment should take patients disease characteristics and comorbidities into account. It may include the use of 5-ASA, but usually consists of immunosuppression with AZA. Alternatively, biologics or small molecules may be considered.

If patients are not responding to IV corticosteroids within 3–5 days, having sustained fever, bloody diarrhea ≥4 times daily, or elevated CRP, rescue therapy with ciclosporin or infliximab must be considered [85, 86]. Only case reports exist for the use of tofacitinib in this clinical scenario [87]. Extending IV corticosteroid ther-

apy beyond 7–10 days has no benefit [84]. The management of acute severe UC must be medico-surgical and requires careful, ongoing clinical evaluation of patients as delayed surgery can increase postoperative complications and mortality after 7 days [88, 89]. However, second-line medical therapy is not associated with higher mortality [83]. Intravenous cyclosporine may be initiated, and trough levels have to be checked on day 3 [90, 91]. Hypocholesterolemia and poor renal function should be excluded prior to starting treatment, and prophylaxis against *Pneumocystis jiroveci* may be installed [92, 93] as a combined immunosuppression entails an increased risk of infection. Short-term response rate to ciclosporin therapy has been reported between 64 and 82% and colectomy rates range from 26 to 47% [94]. In patients who respond to cyclosporine, overlapping AZA/6-MP maintenance therapy should be started before discharge and oral cyclosporine continued for at least 3 month as bridging therapy [95]. In patients with acute severe UC while on therapy with AZA/6-MP respond poorly to treatment with cyclosporine [96, 97] and additionally immunosuppressants are not an option for long-term treatment after discontinuation of cyclosporine.

As an alternative to rescue therapy with cyclosporine, infliximab may be started [98–102]. However, conventional standard dosing schedule for induction therapy may not be ideal, and more intensive dosing strategies have been suggested to adequately reduce colectomy rates in acute severe UC [103]. Intestinal protein loss with rapid clearing of infliximab but also high TNF burden, anti-TNF neutralization, and reduced tissue penetration have all been proposed to attribute to accelerated clearance of anti-TNF drugs [104, 105]. Disease severity is associated with higher levels of serum and mucosal TNF [106]. If no clinical improvement occurs within 7–10 days or a clinical deterioration occurs, surgery must be considered [107]. Current rates of colectomy in acute severe UC treated with infliximab are reported between 35 and 50% [94]. In patients responding to infliximab, combination therapy with AZA can be considered for 6–12 months until durable remission is achieved. Both infliximab and AZA are suitable for maintenance therapy. Tacrolimus may be an alternative in specialized centers [108].

Both cyclosporin and infliximab can be used for rescue therapy. Current data suggest equal efficacy in preventing short-term and long-term colectomy, with similar failure rates [86]. The value of sequential rescue therapy after nonresponse to either infliximab or ciclosporin remains controversial. Although clinical response with sequential therapy showed short-term response rates of 62% and colectomy rates of 28%, the intense immunosuppression leads to serious infections in 7% and the limited data so far do not allow clinical guidance [109]. Sequential therapy should only be performed in specialized centers.

Conclusion

The care for patients suffering from moderate-to-severe UC remains challenging, despite decreasing morbidity and mortality over the past decades. 5-ASA, thiopurines, anti-TNF, and vedolizumab are well-established treatment regimens for induction and maintenance of remission in UC. 5-ASA is considered the standard in treating mild-to-moderate UC, eventually combined oral and rectal. Patients with inadequate response to optimized 5-ASA therapy will escalate to budesonide-MMX or oral prednisone. To induce remission in more severe disease, IV corticosteroids remain the first-line therapy, while cyclosporin and infliximab are the mainstay of rescue therapies in acute severe UC not responding to IV corticosteroids. The early detection of severe flares, more therapeutic options for medical therapy, better intensive care, and improved surgical techniques have led to a significant decrease in morbidity and mortality in acute severe UC. One of the most important factors remains the interdisciplinary teamwork between of gastroenterologist and experienced colorectal surgeons at any time during the clinical course in order to decide upon the best timing for colectomy, which is still required in 30% of the patients.

There are still many open questions and knowledge gaps to be clarified by future research. In the future, upcoming treatment options with different molecular pathways and different modes of actions will further increase the need for personalized medicine. A better understanding of pathophysiological processes, pharmacogenomics, and predictive markers for disease activity will help to identify subpopulations of UC patients who will benefit from tailored treatment regimens to individuals.

Disclosure Statement

E.B. received consultant and/or speaker fees from Abbvie, Janssen, MSD, Norgine, Pfizer, Takeda. M.H.M. received consultant and/or speakers fees and/or grants from Abbvie, Janssen, Lilly, MSD, Pfizer, Takeda, UCB, Vifor. A.M.S. received consultant and/

or speaker fees from the following companies: Abbvie, Janssen, MSD, Pfizer, Takeda, UCB, Vifor. F.S. received consultant and/or speaker fees from the following companies: MSD, Janssen, Pfizer, Takeda. G.V.A. received honoraria or grant support from Abbvie, Ferring, Janssen, Pfizer, Takeda. P.R. received consultant and/or speaker fees from Abbvie, and Amgen. D.L. received consultant and/or speaker fees from Abbvie, Biogaran, Biogen, Ferring, HAC-pharma, Janssen, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag, Tillots. M.M. received consultant and/or speaker fees from Abbvie, Ewopharma AG, MSD, Takeda, and Vifor.

Funding Sources

There are no funding sources to declare.

Author Contributions

E.B., M.H.M.: literature research and drafting the article. M.H.M., A.M.S., F.S., G.V.A., P.R., and D.L.: revising the article critically for important intellectual content.

References

1 Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A–36A.

2 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54 e42; quiz e30.

3 Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007 May; 369(9573):1641–57.

4 Burri E, Beglinger C. The use of fecal calprotectin as a biomarker in gastrointestinal disease. Expert Rev Gastroenterol Hepatol. 2014 Feb;8(2):197–210.

5 Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, Bastien C, Cahn V, Cadiot G, et al. Development and validation of the Nancy histological index for UC. Gut. 2017 Jan;66(1): 43–9.

6 Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, et al. Development and validation of a histological index for UC. Gut. 2017 Jan;66(1):50–8.

7 Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. Clin Gastroenterol Hepatol. 2018;16(3): 343–56.e3.

8 Solberg IC, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, et al.; IBSEN Study Group. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44(4): 431–40.

9 Sjöberg D, Holmström T, Larsson M, Nielsen AL, Holmquist L, Ekbom A, et al. Incidence and clinical course of Crohn's disease during the first year – results from the IBD Cohort of the Uppsala Region (ICURE) of Sweden 2005–2009. J Crohn's Colitis. 2014 Mar;8(3): 215–22.

10 Jeuring SF, Bours PH, Zeegers MP, Ambergen TW, van den Heuvel TR, Romberg-Camps MJ, et al. Disease Outcome of Ulcerative Colitis in an Era of Changing Treatment Strategies: Results from the Dutch Population-Based IBDSL Cohort. J Crohn's Colitis. 2015 Oct;9(10):837–45.

11 Frolkis AD, Dykeman J, Negrón ME, Debruyn J, Jette N, Fiest KM, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterology. 2013 Nov;145(5):996–1006.

12 Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384–413.

13 Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, et al.; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: current Management. J Crohn's Colitis. 2017 Jul;11(7):769–84.

14 Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology. 2015;148(5): 1035–58.e3.

15 Christensen B, Hanauer SB, Erlich J, Kassim O, Gibson PR, Turner JR, et al. Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes. Clin Gastroenterol Hepatol. 2017; 15(10):1557–64.e1.

16 Kanazawa M, Takahashi F, Tominaga K, Abe K, Izawa N, Fukushi K, et al. Relationship between endoscopic mucosal healing and histologic inflammation during remission maintenance phase in ulcerative colitis: a retrospective study. Endosc Int Open. 2019 Apr;7(4): E568–75.

17 Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun;55(6): 749–53.

18 Meucci G, Vecchi M, Astegiano M, Beretta L, Cesari P, Dizioli P, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). Am J Gastroenterol. 2000 Feb;95(2):469–73.

19 Walsh AJ, Bryant RV, Travis SP. Current best practice for disease activity assessment in IBD. Nat Rev Gastroenterol Hepatol. 2016 Oct;13(10):567–79.

20 Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al.; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohn's Colitis. 2017 Jun;11(6):649–70.

21 Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. BMJ. 1955 Oct;2(4947):1041–8.

22 Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010 Jan;(1):CD004115.

23 Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Apr;(2):CD000543.

24 Rubin DT, Cohen RD, Sandborn WJ, Lichtenstein GR, Axler J, Riddell RH, et al. Budesonide Multimatrix Is Efficacious for Mesalamine-refractory, Mild to Moderate Ulcerative Colitis: A Randomised, Placebo-controlled Trial. J Crohn's Colitis. 2017 Jul;11(7): 785–91.

25 Travis SP, Danese S, Kupcinskas L, Alexeeva O, D'Haens G, Gibson PR, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut. 2014 Mar;63(3): 433–41.

26 Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):590–99.

27 Loftus EV Jr, Kane SV, Bjorkman D. Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2004 Jan;19(2):179–89.
28 D'Haens G. Systematic review: second-generation vs. conventional corticosteroids for induction of remission in ulcerative colitis. Aliment Pharmacol Ther. 2016 Nov;44(10):1018–29.
29 Sherlock ME, MacDonald JK, Griffiths AM, Steinhart AH, Seow CH. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2015 Oct;(10):CD007698.
30 Gross V, Bunganic I, Belousova EA, Mikhailova TL, Kupcinskas L, Kiudelis G, et al.; International BUC-57 Study Group. 3g mesalazine granules are superior to 9mg budesonide for achieving remission in active ulcerative colitis: a double-blind, double-dummy, randomised trial. J Crohn's Colitis. 2011 Apr;5(2):129–38.
31 Cohen RD, Dalal SR. Systematic Review: Rectal Therapies for the Treatment of Distal Forms of Ulcerative Colitis. Inflamm Bowel Dis. 2015 Jul;21(7):1719–36.
32 Christophi GP, Rengarajan A, Ciorba MA. Rectal budesonide and mesalamine formulations in active ulcerative proctosigmoiditis: efficacy, tolerance, and treatment approach. Clin Exp Gastroenterol. 2016 May;9:125–30.
33 Travis SP, Stange EF, Lémann M, Oresland T, Bemelman WA, Chowers Y, et al.; European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the management of ulcerative colitis: current management. J Crohn's Colitis. 2008 Mar;2(1):24–62.
34 Ho GT, Chiam P, Drummond H, Loane J, Arnott ID, Satsangi J. The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort. Aliment Pharmacol Ther. 2006 Jul;24(2):319–30.
35 Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al.; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's Colitis. 2014 Jun;8(6):443–68.
36 Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016 May;(5):CD000544.
37 Ford AC, Achkar JP, Khan KJ, Kane SV, Talley NJ, Marshall JK, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):601–16.
38 Mosli MH, MacDonald JK, Bickston SJ, Behm BW, Tsoulis DJ, Cheng J, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis: a Cochrane systematic review and meta-analysis. Inflamm Bowel Dis. 2015 May;21(5):1151–9.
39 Bickston SJ, Behm BW, Tsoulis DJ, Cheng J, MacDonald JK, Khanna R, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2014 Aug;(8):CD007571.
40 Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Aliment Pharmacol Ther. 2018 Jan;47(2):162–75.
41 Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, et al. Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. PLoS One. 2016 Oct;11(10):e0165435.
42 Jonkers D, Penders J, Masclee A, Pierik M. Probiotics in the management of inflammatory bowel disease: a systematic review of intervention studies in adult patients. Drugs. 2012 Apr;72(6):803–23.
43 Karner M, Kocjan A, Stein J, Schreiber S, von Boyen G, Uebel P, et al. First multicenter study of modified release phosphatidylcholine "LT-02" in ulcerative colitis: a randomized, placebo-controlled trial in mesalazine-refractory courses. Am J Gastroenterol. 2014 Jul;109(7):1041–51.
44 Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology. 2015;149(1):110–8.e4.
45 Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology. 2015;149(1):102–9.e6.
46 Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohn's Colitis. 2012 Dec;6(10):965–90.
47 Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology. 2001 Aug;121(2):255–60.
48 Khan N, Abbas A, Williamson A, Balart L. Prevalence of corticosteroids use and disease course after initial steroid exposure in ulcerative colitis. Dig Dis Sci. 2013 Oct;58(10):2963–9.
49 Sewitch MJ, Abrahamowicz M, Barkun A, Bitton A, Wild GE, Cohen A, et al. Patient nonadherence to medication in inflammatory bowel disease. Am J Gastroenterol. 2003 Jul;98(7):1535–44.
50 Kane SV, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. Am J Gastroenterol. 2001 Oct;96(10):2929–33.
51 Lee J, Jee SR, Kim HW, Baek DH, Song GA, Moon W, et al.; Busan Ulsan Gyeongnam Intestinal Study Group Society (BIGS). Factors associated with low adherence to oral 5-aminosalicylic acid in patients with ulcerative colitis. PLoS One. 2019 Mar;14(3):e0214129.
52 Kruis W, Kiudelis G, Rácz I, Gorelov IA, Pokrotnieks J, Horynski M, et al.; International Salofalk OD Study Group. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. Gut. 2009 Feb;58(2):233–40.
53 Wang Y, MacDonald JK, Vandermeer B, Griffiths AM, El-Matary W. Methotrexate for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2015 Aug;(8):CD007560.
54 Carbonnel F, Colombel JF, Filippi J, Katsanos KH, Peyrin-Biroulet L, Allez M, et al.; European Crohn's and Colitis Organisation; Groupe d'Étude Thérapeutique des Affections Inflammatoires Digestives. Methotrexate Is Not Superior to Placebo for Inducing Steroid-Free Remission, but Induces Steroid-Free Clinical Remission in a Larger Proportion of Patients With Ulcerative Colitis. Gastroenterology. 2016 Feb;150(2):380–8.e4.
55 Herfarth H, Barnes EL, Valentine JF, Hanson J, Higgins PD, Isaacs KL, et al.; Clinical Research Alliance of the Crohn's and Colitis Foundation. Methotrexate Is Not Superior to Placebo in Maintaining Steroid-Free Response or Remission in Ulcerative Colitis. Gastroenterology. 2018 Oct;155(4):1098–1108.e9.
56 Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006 Jan;55(1):47–53.
57 Konidari A, Matary WE. Use of thiopurines in inflammatory bowel disease: safety issues. World J Gastrointest Pharmacol Ther. 2014 May;5(2):63–76.
58 Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011 Jan;9(1):36–41.e1.
59 Ariyaratnam J, Subramanian V. Association between thiopurine use and nonmelanoma skin cancers in patients with inflammatory bowel disease: a meta-analysis. Am J Gastroenterol. 2014 Feb;109(2):163–9.
60 Bruns T, Stallmach A. Drug monitoring in inflammatory bowel disease: helpful or dispensable? Dig Dis. 2009;27(3):394–403.
61 Teml A, Schaeffeler E, Herrlinger KR, Klotz U, Schwab M. Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing. Clin Pharmacokinet. 2007;46(3):187–208.

62 Hindorf U, Lindqvist M, Peterson C, Söderkvist P, Ström M, Hjortswang H, et al. Pharmacogenetics during standardised initiation of thiopurine treatment in inflammatory bowel disease. Gut. 2006 Oct;55(10):1423–31.
63 Lee YJ, Hwang EH, Park JH, Shin JH, Kang B, Kim SY. NUDT15 variant is the most common variant associated with thiopurine-induced early leukopenia and alopecia in Korean pediatric patients with Crohn's disease. Eur J Gastroenterol Hepatol. 2016 Apr;28(4):475–8.
64 Jensen CH, Tiu J, Catalanotti JS. Azathioprine-induced pancytopenia with normal TPMT activity presenting with HSV oral ulcers. BMJ Case Rep. 2018;2018bcr-2018-225209.
65 Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. Gastroenterology. 2017;153(3):835–57.e6.
66 Khan KJ, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):630–42.
67 Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):644–59, quiz 660.
68 Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2014 Apr;39(7):660–71.
69 Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med. 2014 May;160(10):704–11.
70 Lv R, Qiao W, Wu Z, Wang Y, Dai S, Liu Q, et al. Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: a meta-analysis. PLoS One. 2014 Jan;9(1):e86692.
71 Panaccione R, Ghosh S, Middleton S, Marquez JR, Scott BB, Flint L, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146(2):392–400.e3.
72 Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al.; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013 Aug;369(8):699–710.
73 Kopylov U, Verstockt B, Biedermann L, Sebastian S, Pugliese D, Sonnenberg E, et al. Effectiveness and Safety of Vedolizumab in Anti-TNF-Naïve Patients With Inflammatory Bowel Disease-A Multicenter Retrospective European Study. Inflamm Bowel Dis. 2018 Oct;24(11):2442–51.
74 Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2017 May;376(18):1723–36.
75 Hanauer S, Panaccione R, Danese S, Cheifetz A, Reinisch W, Higgins PD, et al. Tofacitinib Induction Therapy Reduces Symptoms Within 3 Days for Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol. 2019 Jan;17(1):139–47.
76 Ogata H, Kato J, Hirai F, Hida N, Matsui T, Matsumoto T, et al. Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid-refractory ulcerative colitis. Inflamm Bowel Dis. 2012 May;18(5):803–8.
77 Komaki Y, Komaki F, Ido A, Sakuraba A. Efficacy and Safety of Tacrolimus Therapy for Active Ulcerative Colitis; A Systematic Review and Meta-analysis. J Crohn's Colitis. 2016 Apr;10(4):484–94.
78 Miyoshi J, Matsuoka K, Inoue N, Hisamatsu T, Ichikawa R, Yajima T, et al. Mucosal healing with oral tacrolimus is associated with favorable medium- and long-term prognosis in steroid-refractory/dependent ulcerative colitis patients. J Crohn's Colitis. 2013 Dec;7(12):e609–14.
79 Sands BE, Peyrin-Biroulet L, Loftus EV Jr, Danese S, Colombel JF, Törüner M, et al.; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med. 2019 Sep;381(13):1215–26.
80 van Schaik T, Maljaars JP, Roopram RK, Verwey MH, Ipenburg N, Hardwick JC, et al. Influence of combination therapy with immune modulators on anti-TNF trough levels and antibodies in patients with IBD. Inflamm Bowel Dis. 2014 Dec;20(12):2292–8.
81 Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):96-109.e1.
82 Colombel JF, Sands BE, Rutgeerts P, Sandborn W, Danese S, D'Haens G, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017 May;66(5):839–51.
83 Lynch RW, Lowe D, Protheroe A, Driscoll R, Rhodes JM, Arnott ID. Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. Aliment Pharmacol Ther. 2013 Oct;38(8):935–45.
84 Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol. 2007 Jan;5(1):103–10.
85 Laharie D, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J, et al.; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet. 2012 Dec;380(9857):1909–15.
86 Duijvis NW, Ten Hove AS, Ponsioen CI, van den Brink GR, Buskens CJ, Bemelman WA, et al. Similar Short- and Long-term Colectomy Rates with Ciclosporin and Infliximab Treatment in Hospitalised Ulcerative Colitis Patients. J Crohn's Colitis. 2016 Jul;10(7):821–7.
87 Berinstein JA, Steiner CA, Regal RE, Allen JI, Kinnucan JA, Stidham RW, et al. Efficacy of Induction Therapy With High-Intensity Tofacitinib in 4 Patients With Acute Severe Ulcerative Colitis. Clin Gastroenterol Hepatol. 2019 Apr;17(5):988–990.e1.
88 Randall J, Singh B, Warren BF, Travis SP, Mortensen NJ, George BD. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. Br J Surg. 2010 Mar;97(3):404–9.
89 Kaplan GG, McCarthy EP, Ayanian JZ, Korzenik J, Hodin R, Sands BE. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. Gastroenterology. 2008 Mar;134(3):680–7.
90 Van Assche G, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology. 2003 Oct;125(4):1025–31.
91 Arts J, D'Haens G, Zeegers M, Van Assche G, Hiele M, D'Hoore A, et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. Inflamm Bowel Dis. 2004 Mar;10(2):73–8.
92 Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. Am J Gastroenterol. 1999 Jun;94(6):1587–92.
93 Epple HJ. Therapy- and non-therapy-dependent infectious complications in inflammatory bowel disease. Dig Dis. 2009;27(4):555–9.
94 Seah D, De Cruz P. Review article: the practical management of acute severe ulcerative colitis. Aliment Pharmacol Ther. 2016 Feb;43(4):482–513.
95 Ng SC, Kamm MA. Therapeutic strategies for the management of ulcerative colitis. Inflamm Bowel Dis. 2009 Jun;15(6):935–50.
96 Moskovitz DN, Van Assche G, Maenhout B, Arts J, Ferrante M, Vermeire S, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. Clin Gastroenterol Hepatol. 2006 Jun;4(6):760–5.

97 Moss AC, Peppercorn MA. Steroid-refractory severe ulcerative colitis: what are the available treatment options? Drugs. 2008; 68(9):1157–67.
98 Ferrante M, Vermeire S, Katsanos KH, Noman M, Van Assche G, Schnitzler F, et al. Predictors of early response to infliximab in patients with ulcerative colitis. Inflamm Bowel Dis. 2007 Feb;13(2):123–8.
99 Gisbert JP, González-Lama Y, Maté J. Systematic review: infliximab therapy in ulcerative colitis. Aliment Pharmacol Ther. 2007 Jan;25(1):19–37.
100 Jakobovits SL, Jewell DP, Travis SP. Infliximab for the treatment of ulcerative colitis: outcomes in Oxford from 2000 to 2006. Aliment Pharmacol Ther. 2007 May;25(9): 1055–60.
101 Järnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology. 2005 Jun;128(7):1805–11.
102 Lees CW, Heys D, Ho GT, Noble CL, Shand AG, Mowat C, et al.; Scottish Society of Gastroenterology Infliximab Group. A retrospective analysis of the efficacy and safety of infliximab as rescue therapy in acute severe ulcerative colitis. Aliment Pharmacol Ther. 2007 Aug;26(3):411–9.
103 Gibson DJ, Heetun ZS, Redmond CE, Nanda KS, Keegan D, Byrne K, et al. An accelerated infliximab induction regimen reduces the need for early colectomy in patients with acute severe ulcerative colitis. Clin Gastroenterol Hepatol. 2015;13(2):330–5.e1.
104 Rosen MJ, Minar P, Vinks AA. Review article: applying pharmacokinetics to optimise dosing of anti-TNF biologics in acute severe ulcerative colitis. Aliment Pharmacol Ther. 2015 Jun;41(11):1094–103.
105 Dotan I, Ron Y, Yanai H, Becker S, Fishman S, Yahav L, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. Inflamm Bowel Dis. 2014 Dec;20(12):2247–59.
106 Olsen T, Goll R, Cui G, Husebekk A, Vonen B, Birketvedt GS, et al. Tissue levels of tumor necrosis factor-alpha correlates with grade of inflammation in untreated ulcerative colitis. Scand J Gastroenterol. 2007 Nov;42(11): 1312–20.
107 Mañosa M, López San Román A, Garcia-Planella E, Bastida G, Hinojosa J, Gonzalez-Lama Y, et al. Infliximab rescue therapy after cyclosporin failure in steroid-refractory ulcerative colitis. Digestion. 2009;80(1): 30–5.
108 Baumgart DC, Macdonald JK, Feagan B. Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis. Cochrane Database Syst Rev. 2008 Jul;(3): CD007216.
109 Narula N, Fine M, Colombel JF, Marshall JK, Reinisch W. Systematic Review: Sequential Rescue Therapy in Severe Ulcerative Colitis: Do the Benefits Outweigh the Risks? Inflamm Bowel Dis. 2015 Jul;21(7): 1683–94.