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REVIEW

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Practical management of mild-to-moderate ulcerative colitis: an international expert consensus

Ferdinando D'Amico[a], Fernando Magro[b], Axel Dignass[c], Sameer Al Awadhi[d], Ana Gutierrez Casbas[e,f], Natália Sousa Freitas Queiroz[g], Grażyna Rydzewska[h], Byong Duk Ye[i], Zhihua Ran[j], Ailsa Hart[k], Vipul Jairath[l], Gionata Fiorino[m], Laurent Peyrin-Biroulet[n,o,p,q,r,s] and Silvio Danese[a,t]

[a]Gastroenterology and Endoscopy, IRCCS San Raffaele Hospital, Milan, Italy; [b]CINTESIS@RISE, Faculty of Medicine, The University of Porto, Porto, Portugal; [c]Department of Medicine I, Agaplesion Markus Hospital, Goethe University, Frankfurt/Main, Germany; [d]Digestive Diseases Unit, Rashid Hospital, Dubai Health, UAE; [e]Department of Gastroenterology, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, España; [f]Department of Gastroenterology, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, España; [g]Gastroenterology Unit, Santa Cruz Hospital, Curitiba, Brazil; [h]Department of Gastroenterology and Internal Medicine, National Medical Institute of Ministry of Interior and Administration, Warsaw, Poland; [i]Department of Gastroenterology and Inflammatory Bowel Disease Center, AsanMedical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [j]Department of Gastroenterology Zhou Pu Hospital, Shanghai University of Medicine & Health Sciences, Shanghai, China; [k]Inflammatory Bowel Disease Unit, St Mark's Hospital, London, UK; [l]Departments of Gastroenterology and Medicine, Western University Schulich School of Medicine & Dentistry, London, Ontario, Canada; [m]IBD Unit, Department of Gastroenterology and Digestive Endoscopy, San Camillo-Forlanini Hospital, Rome, Italy; [n]Department of Gastroenterology, Nancy University Hospital, Vandœuvre-lès-Nancy, France; [o]Department of Gastroenterology, Inserm, NGERE, University of Lorraine, Nancy, France; [p]Department of Gastroenterology, INFINY Institute, Nancy University Hospital, Vandœuvre-lès-Nancy, France; [q]Department of Gastroenterology, FHU-CURE, Nancy University Hospital, Vandœuvre-lès-Nancy, France; [r]Department of Gastroenterology, Groupe Hospitalier privé Ambroise Paré - Hartmann, Paris IBD center, Neuilly sur Seine, France; [s]Department of Gastroenterology, Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, QC, Canada; [t]Gastroenterology and Endoscopy, Vita-Salute San Raffaele University, Milan, Italy

ABSTRACT

Introduction: Although there are well-defined guidelines for the management of mild-to-moderate ulcerative colitis (UC), there are still unmet needs. For this reason, we conducted an international expert consensus to standardize the management of patients with mild-to-moderate UC and provide practical guidance to clinicians.

Areas covered: Based on Delphi methodology, 15 statements were approved after two rounds of voting, addressing several aspects of disease management from sequencing to treatment duration, from monitoring to optimization techniques and safety profile.

Expert opinion: Growing knowledge of mild-to-moderate UC has led to the development of new ambitious outcomes such as histological remission and disease clearance. Furthermore, noninvasive tools for patient monitoring such as fecal calprotectin and intestinal ultrasound are now available. Their implementation in clinical practice will allow clinicians to tightly monitor disease activity and promptly adapt treatment, avoiding complications and disease progression and targeting better disease control.

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Ulcerative colitis; inflammatory bowel disease; mesalamine; 5-ASA; budesonide MMX

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that negatively impacts patients' quality of life [1]. It is estimated that approximately 400 of every 100,000 people in North America are affected by UC and its prevalence is continually increasing [2]. Disease severity ranges from mild to severe, two-thirds of patients are reported to have mild-to-moderate disease during the first year after diagnosis [3]. Mesalamine (5-ASA) is recommended by several international guidelines as a first-line therapy for the treatment of mild-to-moderate UC, while corticosteroids are generally preferred as a second-line [4–7]. However, not all patients treated with 5-ASA achieve optimal disease control [8]. Several factors can influence treatment results, including the administration route, induction and maintenance dosages, timing and type of monitoring, optimization or possible de-escalation. For this reason, we conducted an international expert consensus meeting to standardize the management of patients with mild-to-moderate UC and define optimization and monitoring strategies.

2. Methods

Three authors (FD, LPB, and SD) conducted an extensive search of PubMed, Embase, and Web of Science databases up to April 2024 to identify all studies evaluating the management of adult patients with mild-to-moderate UC. The following search terms were used: 'mesalazine,' 'mesalamine,' '5-ASA,' 'aminosalicylates,' 'budesonide

CONTACT Silvio Danese sdanese@hotmail.com Gastroenterology and Endoscopy IRCCS San Raffaele Hospital and Vita-Salute, San Raffaele University, Via Olgettina 60, Milan, Italy

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Article highlights

- This international expert consensus standardizes the management of patients with mild-to-moderate UC providing practical guidance to clinicians.
- 5-ASA therapy is the first-line therapy for the treatment of mild to moderate UC.
- Budesonide MMX should be considered as an add-on therapy in patients who do not respond to 5-ASA therapy.
- Fecal calprotectin is a key tool for monitoring disease activity and response to therapy.
- Non-invasive disease monitoring and timely-dose adjustment allow optimal control of mild to moderate UC.

MMX,' 'cortiment,' 'second-generation steroids,' 'ulcerative colitis,' 'UC,' 'inflammatory bowel disease,' 'IBD,' 'mild-to-moderate,' 'induction,' 'maintenance,' 'oral,' 'rectal,' 'monitoring,' 'follow-up,' 'dose escalation,' and 'optimization.' Only studies considered relevant by the authors were taken into consideration. From the literature review, three authors (FD, LPB, and SD) created 13 initial statements about the management of patients with mild-to-moderate UC, which are detailed in Supplementary Table S1. The statements were focused on the management of two main scenarios: 1) patient naive to any therapy; 2) patient on 5-ASA therapy (maintenance dosage <4 g/day) experiencing a disease flare. These statements were reviewed by a panel of 14 experts (FD, FM, AD, NSFQ, SAA, AGC, RZ, BDY, AH, GR, VJ, GF, LPB, SD) from 12 countries (Brazil, Canada, China, France, Germany, Italy, Korea, Poland, Portugal, Spain, United Arab Emirates, and United Kingdom). Only physicians managing over 2000 patients with IBD annually were invited to participate, ensuring a high level of expertise. A two-step procedure was applied. First, the statements were voted (agree or disagree) anonymously online according to a well-known Delphi methodology. A statement required at least 75% consensus agreement to be accepted. The statements that did not reach this threshold during the first round of voting were discussed during a virtual meeting held on 8 May 2024, and subsequently amended. The statements were voted on again in a second round. Statements not achieving consensus after the second round were definitively rejected. Experts could also propose new statements, which were discussed and voted on using the same method. All experts collaborated on drafting the manuscript, which was reviewed and approved by all authors. This process ensured that the recommendations were evidence-based and reflected a broad range of clinical experience and insights from leading experts in the field.

3. Results

3.1. Statements

Twelve statements were approved after the first voting round and one statement after the second round. Two new statements were proposed during the virtual meeting and approved after the first vote, ultimately leading to the approval of 15 statements (Table 1).

3.1.1. Scenario 1: patient naive to any therapy

Statement 1: We recommend the combination of oral 5-ASA (from 2,0 to 4,8 g/day) and rectal 5-ASA (suppository 1 g/day for proctitis and enema ≥1 g/day for left-sided UC/pancolitis) for 8 weeks to induce remission.

5-ASA is the standard treatment for inducing remission in patients with mild to moderate UC naive to any therapy [4–7]. Numerous meta-analyses have confirmed the efficacy of 5-ASA in this context [9–12]. Furthermore, evidence indicates that combining oral and rectal 5-ASA is more effective at inducing remission than using oral therapy alone [9,10,13]. Despite this, there is no consensus on the optimal type and dosage of 5-ASA. No significant differences in remission rates are reported among the different oral 5-ASA formulations [11]. However, a randomized clinical trial comparing high (4.8 g/day) and low (2.4 g/day) doses of oral 5-ASA showed a higher induction of remission rate with a higher dose (43% vs. 35%, *p*

Table 1. Approved statements and agreement after the second round of voting.

	Statements	Agreement >75% (%)
1	We recommend the combination of oral 5-ASA (from 2,0 to 4,8 g/day) and rectal 5-ASA (suppository 1 g/day for proctitis and enema ≥1 g/day for left-sided UC/pancolitis) for 8 weeks to induce remission.	100%
2	Response to induction treatment should be monitored clinically and by fecal calprotectin	100%
3	Fecal calprotectin measurement should be performed after 8-12 weeks of induction therapy with 5-ASA	100%*
4	In patients achieving clinical response after induction therapy with 5-ASA, we recommend monitoring fecal calprotectin every 3-6 months	90%*
5	In case of inadequate response after two to four weeks of treatment, we recommend optimizing medical therapy.	100%*
6	In patients who respond to induction therapy we recommend continuing oral therapy with 5-ASA at a maintenance dosage (2,0-2,4 g/day)	92.9%
7	In patients who do not respond to induction therapy we recommend budesonide MMX (9 mg/day) as add-on therapy for 8 weeks.	85.7%
8	We recommend performing an endoscopic evaluation within 6 to 12 months of starting 5-ASA therapy.	85.7%
9	We recommend once-daily administration of oral 5-ASA to improve adherence to therapy.	100%
10	We recommend monitoring renal function every 6 months in all patients treated with oral 5-ASA.	78.6%
11	In patients experiencing clinical, biochemical, ultrasound, or endoscopic flare of disease, we recommend optimizing oral 5-ASA (≥4 g/day) for 8 weeks and to add rectal 5-ASA.	100%
12	In patients who do not respond to optimized 5-ASA therapy, we recommend performing stool tests to exclude intestinal infections before starting steroid therapy.	100%
13	In patients who respond to optimized oral 5-ASA (≥4 g/day) and experience a loss of response upon de-escalation (<4 g/day), 5-ASA should be re-escalated (≥4 g/day) and maintained at stable dosage.	92.9%
14	We recommend performing an endoscopic evaluation 6-12 months after therapy optimization.	92.9%
15	Oral 5-ASA should be continued as long-term maintenance therapy to prevent the risk of colorectal cancer.	100%

*After the second round of voting.

= 0.04) [14]. Another clinical trial confirmed that a higher dose (4.8 g per day) led to endoscopic remission (endoscopic Mayo score ≤1) more frequently than a lower dose (2.4 g per day) (80% vs. 68%, $p = 0.012$) [15]. In terms of rectal therapy, no differences in efficacy were found between three different dosages of 5-ASA enemas (1 g, 2 g, and 4 g per day), suggesting that a 1-g enema is sufficient for managing symptoms in patients with left-sided UC or pancolitis [16]. For proctitis, 1 g 5-ASA suppositories are effective and preferred by patients over the 500 mg formulations, which require more frequent administration [17,18]. When selecting a 5-ASA dosage to induce remission, factors such as patient preference, disease extent, and severity should be considered. A dosage of at least 2 g per day orally might be appropriate for proctitis and patients with slightly increased bowel movements and occasional rectal bleeding, while more extensive disease or those with a severe activity, as indicated by the Mayo score, may require a higher dose (≥4 g).

Statement 2: Response to induction treatment should be monitored clinically and by fecal calprotectin.

Treatment targets have evolved over the past 10 years including not only clinical improvement and remission but also endoscopic remission and normalization of inflammatory biomarkers, such as fecal calprotectin and C-reactive protein (CRP) [19]. Unfortunately, endoscopic evaluation is not always feasible in clinical practice at the end of the induction phase due to long waiting lists and due to their invasive nature for patient tolerability. Low CRP values are associated with a reduced risk of clinical relapse and normalization of CRP is considered a short- and intermediate-term treatment target in UC [19]. Fecal calprotectin is an accurate noninvasive biomarker, which correlates with endoscopic and histological activity and allows the response to therapy to be assessed [20,21]. To date, a universally accepted fecal calprotectin cutoff for remission is not yet available. However, a value between 100 and 250 µg/g is generally considered valid for distinguishing disease activity and remission [19]. A post-hoc analysis of data from a phase 3 non-inferiority trial of 726 adults with mild-to-moderate UC treated with 5-ASA showed that 50% reduction in fecal calprotectin from baseline and reduction in rectal bleeding predicted endoscopic improvement at week 8 [22]. Of note, in a randomized study conducted on patients with mild to moderate UC, 5-ASA therapy was optimized (in the experimental group) if the fecal calprotectin value was higher than 300 µg/g, while it remained unchanged in the control group. Patients optimized based on fecal calprotectin had a lower risk of disease recurrence (28.6% and vs 57.1%, $p < 0.05$) supporting the use of fecal calprotectin in disease monitoring [23]. The combination of fecal calprotectin and clinical evaluation can therefore allow an adequate evaluation and thereby enable a timely and appropriate therapeutic decision. A decision analytical Markov model compared a treat-to-target approach based on symptom control and normalization of fecal calprotectin to a symptom-only strategy in patients with mild-to-moderate UC [24]. Interestingly, the model based on the combination of symptoms and biomarkers was associated with a reduced risk of relapse and increased time spent by the patient in clinical remission, albeit was associated with higher pecuniary costs. An ongoing pragmatic randomized controlled trial will prospectively compare management based on clinical evaluation alone versus tight monitoring of symptoms and fecal calprotectin, clarifying whether this strategy allows for better disease control [25].

Statement 3: Fecal calprotectin measurement should be performed after 8-12 weeks of induction therapy with 5-ASA.

The CALM study was the first randomized clinical trial to demonstrate that a strategy based on clinical assessment and measurement of fecal calprotectin (every 3 months) was associated with better clinical and endoscopic outcomes in Crohn's disease compared to a strategy guided only by symptoms [26]. Similar studies in UC have not yet been published and there is no standardization regarding the timing of fecal calprotectin measurement. However, measurement of fecal calprotectin at the end of induction therapy predicts clinical and endoscopic remission at one year, thus representing a very important time-point for identifying patients at risk of non-response to therapy and for timely treatment adjustment [27,28]. In a study conducted in patients in remission, those who had fecal calprotectin values >100 µg/g had an increased risk of relapse [29]. Fecal calprotectin could also allow stratification of patients who are candidates for de-escalation of therapy. It should be underlined that several pre-analytical (e.g. collection time, stool consistency, storage and extrapolation methods) and analytical (e.g. concomitant intake of anti-inflammatory drugs or proton pump inhibitors or other disease) factors can influence fecal calprotectin concentrations making its accurate interpretation essential [30].

Statement 4: In patients achieving clinical response after induction therapy with 5-ASA, we recommend monitoring fecal calprotectin every 3-6 months.

Clinical response is generally defined as at least 50% reduction in the number of bowel movements and rectal bleeding compared to baseline [19]. Clinical response is a valuable short-term target in UC but cannot be considered a long-term target. For this reason, in patients with persistent symptoms it is recommended to perform a tight monitoring using fecal calprotectin to monitor the response to therapy and predict worsening of symptoms. The American Gastroenterological Association (AGA) guideline recommends monitoring fecal calprotectin every 6 to 12 months in patients who achieve clinical remission [31]. It is therefore plausible that in patients who have had a partial response to treatment monitoring should be more frequent (around 3–6 months based on disease severity).

Statement 5: In case of inadequate response after two to four weeks of treatment, we recommend optimizing medical therapy.

UC can be a progressive disease in some patients as, if not well controlled, it is associated with the risk of hospitalization, surgery, and neoplasia [32,33]. The 5-ASA generally requires 2–4 weeks to achieve clinical response and can induce endoscopic remission after 4 weeks in up to two-thirds of cases [34]. Tight monitoring of patients is essential for timely therapy adjustment and prevention of any complications. For this reason, in case of persistent rectal bleeding causing anemia or iron deficiency or in case of persistent increase in inflammatory indices, early optimization is recommended [35]. High doses of 5-ASA (≥4 g/day) and the combination of oral and rectal 5-ASA have been shown to allow faster achievement of clinical and endoscopic response compared to low doses or oral therapy alone [36–38]. An open-label phase 3b/4 study demonstrated that patients with UC who did not achieve remission after 8 weeks with high-dose 5-ASA (≥4 g/day) were less likely to be in remission if they were treated with low doses of 5-ASA (<4 g/day) during maintenance [39]. Of note, several factors must be considered in case of non-response to treatment including compliance with therapy. Factors associated with non-compliance include poor compliance, lack of belief in the drug effectiveness, and concerns about risk and side effects [40]. A key role is therefore played by physician-patient communication. Reinforcing the importance of compliance becomes part of the treatment.

Statement 6: In patients who respond to induction therapy, we recommend continuing oral therapy with 5-ASA at a maintenance dosage (2,0-2,4 g/day).

There is evidence that 5-ASA is more effective than placebo in maintaining disease remission [41]. For this reason, it is recommended that 5-ASA be continued as a long-standing therapy. A Markov Model compared two strategies for the management of UC patients in remission: to discontinue 5-ASA or to continue 5-ASA 2 g per day as maintenance [42]. This analysis showed a clear reduction in the risk of recurrence during a two-year follow-up. Moreover, in patients with UC in remission, no difference in terms of disease recurrence was reported between those treated with low (1.5 g per day) and high (3 g per day) doses of oral 5-ASA ($p = 0.057$), supporting the use of minimum effective dosage [43]. On the other hand, patients with extensive UC and those who experience frequent relapses might benefit from maintenance with high doses of the drug [44]. No differences were identified between oral mesalamine formulations (sustained release, delayed release, and prodrugs) used in randomized clinical trials [45].

Statement 7: In patients who do not respond to induction therapy we recommend budesonide MMX (9 mg/day) as an add-on therapy for 8 weeks.

Steroid therapy should be considered in patients who do not respond to optimized 5-ASA therapy [5–7]. Several formulations are available, including oral and rectal formulations. However, systemic steroids can cause several side effects [46]. For this reason, their use is recommended for severe disease, and it should be used for the shortest possible time and at the lowest effective dosage. Budesonide is a steroid with a first-pass hepatic metabolism resulting in minimal systemic bioavailability and thus side effects. A formulation of budesonide using a multimatrix system (MMX) technology allows delivery of the drug to the colon and has been found to be effective in patients with UC [47]. A randomized controlled trial demonstrated that budesonide MMX 9 mg/day was more effective than placebo in determining clinical disease remission after 8 weeks of treatment (17.9%, vs 7.4%, respectively, $p = 0.0143$) with comparable safety profiles [47]. Similarly, another randomized study confirmed that patients treated with budesonide MMX 9 mg/day had significantly higher clinical and endoscopic remission rates compared with placebo (odds ratio 4.49; 95% CI 1.47 to 13.72; $p = 0.0047$) [48]. The proportion of patients achieving histological remission was also higher among patients treated with budesonide MMX compared to placebo (16.5% vs 6.7%, $p = 0.0361$) supporting its use. Moreover, there is evidence that in patients refractory to 5-ASA, the addition of budesonide MMX is associated with a greater probability of achieving combined clinical and endoscopic remission compared to 5-ASA alone (13.0% vs 7.5% $p = 0.049$) [49]. The role of budesonide MMX as an add on therapy to 5-ASA was also supported by a prospective observational study which compared the efficacy of budesonide MMX monotherapy versus combined use of 5-ASA and budesonide MMX (added within 14 [early add-on] or after 14 [late add-on] days from the start of therapy) [50]. Patients treated with the combination of steroid and mesalamine achieved a higher percentage of clinical remission (57.1% [late add-on] and 52.7% [early add-on] vs 33.3% with monotherapy, $p < 0.05$). Importantly, no increased risk of adverse events occurred with the combination therapy.

Statement 8: We recommend performing an endoscopic evaluation within 6 to 12 months of starting 5-ASA therapy.

Endoscopic remission is still the main long-term therapeutic target in patients with UC [19]. Achieving endoscopic remission reduces the risk of recurrence and the risk of hospitalizations and surgery [51,52]. For this reason, adequate endoscopic monitoring is necessary in order to evaluate disease activity and promptly adapt treatment. An early endoscopic evaluation as well as a delayed one could be associated with an inadequate assessment of the response to therapy leading to suboptimal disease control. Endoscopic monitoring should be performed within 6 months of starting new therapy [53]. However, the timing of endoscopic procedures should vary based on clinical activity and fecal calprotectin levels. In case of persistent activity, endoscopy should be performed sooner while in those who are in clinical remission with normalization of inflammatory markers it could reasonably be performed within 12 months. Importantly, sigmoidoscopy is highly correlated with colonoscopy for evaluating disease activity [54,55]. Therefore, except for colorectal cancer surveillance, sigmoidoscopy could be the preferred option to evaluate response to treatment.

Statement 9: We recommend once-daily administration of oral 5-ASA to improve adherence to therapy.

Poor adherence to oral therapy is one of the main reasons for the ineffectiveness of 5-ASA therapy, resulting in an increased risk of recurrence and higher healthcare costs [56,57]. A complex and fractionated mode of administration can significantly reduce adherence to therapy [58]. For this reason, simplification of administration is one of the solutions to adherence issues by supporting once daily administration. The level of information provided to the patient, the administration route, and the patient's preferences also play a key role in maximizing treatment compliance [59–61]. A meta-analysis of randomized controlled trials investigated any differences in terms of efficacy and safety of once daily versus twice daily 5-ASA in patients with mild-to-moderate UC. Importantly, the percentage of patients achieving clinical and endoscopic remission and the safety profile were comparable between the two strategies [62]. Another randomized study compared once daily and three times a day administrations [63]. The efficacy of once-daily administration was not inferior to the alternative approach, but the once-daily option was preferred by most patients.

Statement 10: We recommend monitoring renal function every 6 months in all patients treated with oral 5-ASA.

Although 5-ASA is a drug with a reassuring safety profile, some cases of nephrotoxicity have been reported. Therefore, renal function monitoring is crucial to identify any impairment early and avoid irreversible damage [64]. Several studies have addressed this topic and no correlation has been identified between the formulation, duration or dosage of 5-ASA and the risk of renal toxicity [65–67]. It is legitimate to hypothesize that this is an idiosyncratic damage that does not depend on drug dose requiring periodic follow-up. The absence of monitoring of renal function is associated with an increased risk of acute kidney impairment [68]. To date, there is no standardization for renal monitoring. However, the use of serum creatinine with estimation of the glomerular filtration rate and urinalysis are the most frequently used tests [64]. As regards the timing of monitoring, a six-monthly evaluation is frequently performed, even if there are no globally accepted guidelines and several factors should be considered for a personalized approach (e.g. age, renal comorbidity, or concomitant therapy with other nephrotoxic drugs) [64,69,70].

3.1.2. Scenario 2: patient under 5-ASA therapy (maintenance dosage <4 g/day) experiencing a disease flare

Statement 11: In patients experiencing clinical, biochemical, ultrasound, or endoscopic flare of disease, we recommend optimizing oral 5-ASA (≥4 g/day) for 8 weeks and to add rectal 5-ASA.

Up to 70% of the patients experience disease recurrence during the first year of treatment with 5-ASA [71]. Tight monitoring is therefore necessary to optimize treatment early and avoid disease progression. Non-invasive tools such as fecal calprotectin and intestinal ultrasound can predict the endoscopic evaluation avoiding early and unnecessary examinations [31,72]. A fecal calprotectin value >150 µg/g or a bowel wall thickness >3 mm could be indicators of disease activity and guide therapeutic decisions together with clinical evaluation [31,73]. In patients with UC experiencing a disease relapse, high doses of 5-ASA (≥4 g/day) may be associated with a greater success rate than low doses (<4 g/day) (72% vs. 58%, respectively, $p < 0.05$) and to a lower risk of hospitalization and surgery [74]. A decision tree model including 10,000 patients with UC revealed that optimizing 5-ASA therapy (defined as maximizing oral therapy or combining rectal and oral therapy) led to a lower risk of recurrence and a considerable cost savings compared to maintenance dosing of 5-ASA, supporting an optimized strategy [75].

Statement 12: In patients who do not respond to optimized 5-ASA therapy, we recommend performing stool tests to exclude intestinal infections before starting steroid therapy.

Steroids are associated with an increased risk of infections and serious infections [46,76,77]. Furthermore, an infection could cause the non-response to therapy and lead to misdiagnosis or overtreatment [78]. Before starting steroid therapy, it is therefore necessary to carry out screening to exclude bacterial, parasitic and Clostridium difficile infections [79]. Other differential diagnoses (e.g. irritable bowel syndrome or drug-induced colitis) should also be taken into account and excluded to ensure a specific and targeted treatment [80,81].

Statement 13: In patients who respond to an optimized oral 5-ASA (≥4 g/day) and experience a loss of response upon de-escalation (<4 g/day), 5-ASA should be re-escalated (≥4 g/day) and maintained at a stable dosage.

Treatment optimization with oral 5-ASA is generally the first step in patients who have a loss of response during the maintenance phase (<4 g/day) [35]. This strategy allows clinical and endoscopic remission to be achieved again in a considerable percentage of patients (44% and 28% respectively) [82]. A multicenter retrospective study investigated the efficacy of high-dose oral 5-ASA (≥4 g/day) as a maintenance therapy in patients who responded to induction phase [83]. Of note, the longer the duration with high-dose 5-ASA, the lower the risk of relapse. In addition, a lower risk of flare has been reported in patients treated with high doses of oral 5-ASA (≥4 g/day) compared with low doses (2-<4 g/day) (26.6% vs 62.5%, $p = 0.04$) supporting the use of high-dose 5-ASA as long-term maintenance therapy in patients at risk of relapse [84].

Statement 14: We recommend performing an endoscopic evaluation 6–12 months after therapy optimization.

The timing of endoscopic reevaluation is a crucial topic for the management of patients with UC. The decision depends

on several factors, including the minimum time needed for the drug to provide benefits [85]. Furthermore, patient tolerability and waiting lists for endoscopic procedures cannot be neglected either. Although noninvasive tools exist for disease monitoring, discrepancies persist between the outcomes assessed [86,87]. For this reason, endoscopy remains a necessary examination to guide therapeutic decisions and ensure effective and timely therapeutic adjustment in case of persistent disease activity. Importantly, endoscopy also allows biopsies to be taken and histological disease activity to be evaluated. Histological remission is increasingly emerging as a determining factor in the long-term prognosis of patients. In fact, histological remission reduces the risk of recurrence and is associated with a lower rate of hospitalization and surgery compared to those who have histological activity [51,88]. Although histology is not yet formally a therapeutic target, it may be useful to guide clinicians in therapeutic decisions regarding possible de-escalation [19].

Statement 15: Oral 5-ASA should be continued as long-term maintenance therapy to prevent the risk of colorectal cancer.

5-ASA has anti-inflammatory properties but also interferes with mechanism implicated in the genesis of colorectal cancer such as cell cycle progression, scavenging of reactive oxygen- or nitrogen-derived metabolites, TNF-alpha/TGF-ss signaling, and WNT/beta-catenin signaling [89]. An older British epidemiological study including almost 20,000 patients reported a reduced risk of colorectal cancer among patients treated with 5-ASA compared to non-users (adjusted OR 0.60, 95% CI 0.38–0.96) [90]. Similarly, a meta-analysis of observational studies identified the use of 5-ASA as a protective factor against the development of colorectal cancer in patients with IBD (pooled odds ratio, 0.51; 95% confidence interval, 0.39–0.66), justifying its use as long-term therapy [91]. This gives 5-ASA an even more important role in the management of patients with mild-to-moderate UC, as not only does it provide effective disease control, it also has an oncoprophylactic effect.

4. Conclusion

Mild-to-moderate UC continues to have several unmet management needs. This international expert consensus provides guidance for clinicians for therapy selection, tight monitoring, and timely optimization.

5. Expert opinion

The management of patients with UC has changed significantly in the last 30 years with the development of new advanced therapies and the evolution in treatment targets [5,19]. Although medications for the treatment of mild-to-moderate UC are unchanged, there have been many innovations in this context as well. In fact, new formulations of 5-ASA allow the daily quantity to be taken in a single solution, while novel delivery systems, such as microparticles, nanoparticles, and hydrogels, will improve controlled release systems and drug bioavailability [92,93]. Disease control is increasingly associated with a patient-centered strategy and tight disease monitoring [94]. Adequate patient information and engagement are essential for this approach in order to proceed with the early and autonomous escalation of medical therapy. A randomized clinical trial compared management based on patient therapy training and follow-up on request with a conventional approach [95]. Patients in the experimental group were treated earlier compared to the control arm (mean of 14.8 hours vs 49.6 hours, respectively, 95% CI 16.4–60.2) and underwent significantly fewer visits to hospital (0.9 vs 2.9 per patient per year, 95% CI 1.6–2.7). As regards patient monitoring, fecal calprotectin plays a predominant role. One of the major limitations to adherence to fecal calprotectin measurement is the need to collect the stool sample and take it to the laboratory [30]. New tests that allow home measurement of fecal calprotectin are available; these are accurately correlated to traditional tests for measuring fecal calprotectin [96–98]. Although their use in clinical practice is still limited, they could allow, after adequate patient training, to monitor the disease, identify any relapses early, and adapt therapy accordingly. In addition, intestinal ultrasound is increasingly recognized as an essential noninvasive tool for monitoring patients with UC and allows evaluating disease activity and response to treatments and predicting endoscopy and risk of recurrence [87]. An ongoing randomized clinical trial will compare two treat-to-target strategies, one based on symptom control, fecal calprotectin, and intestinal ultrasound and one based on endoscopic evaluation (NCT05735665). This study will allow a better understanding of the role of intestinal ultrasound and define whether it can be considered a new treatment target in UC, reducing the need for endoscopic procedures. A frequently reported limitation of intestinal ultrasound is the difficult evaluation of the rectal wall. However, transperineal ultrasound, a tool generally used for the assessment of perianal disease, has been shown to be accurate in predicting endoscopic and histological activity in patients with UC and rectal involvement [99]. Transperineal ultrasound can also predict clinical response to therapy. A Japanese observational study revealed that transperineal ultrasound remission at one week of starting therapy was associated with clinical remission at 8 weeks (adjusted odds ratio 1.90, 95% CI, 1.22–2.95), facilitating the decision-making process [100]. In the field of mild to moderate UC, there are still some aspects that deserve to be explored. A new concept called disease clearance, a composite endpoint including the simultaneous achievement of clinical, endoscopic and histological remission, has been proposed to raise the bar in mild-to-moderate UC, achieving deeper and longer-lasting remission [101]. This ambitious outcome has been also evaluated in patients with mild to moderate UC treated with 5-ASA with results comparable to those of advanced therapies, suggesting that it is achievable with conventional drugs [102]. Furthermore, there is still heterogeneity on the definition of mild to moderate UC [103]. A recent expert consensus provided a definition of mild to moderate UC for clinical trials based on clinical symptoms (rectal bleeding of at least one according to the Mayo sore) and endoscopic symptoms (endoscopic Mayo of at least 2) [104]. However, there is no commonly accepted definition in clinical practice. Furthermore,

disease activity in UC is generally defined as mild-moderate, while there should be a clear distinction between mild disease (the subject of our consensus) and moderate disease, which often requires treatment with immunosuppressive or advanced therapies. The growing knowledge of UC requires the implementation of new outcomes, new monitoring methods, and new optimization strategies in patients with mild-to-moderate disease, improving patients' quality of life and allowing better disease control.

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Author's contributions

S Danese and L Peyrin-Biroulet conceived the study. F D'Amico contributed to manuscript drafting and created tables. All authors critically reviewed the content of the paper and discussed the statements and contributed to the final manuscript.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Gionata Fiorino http://orcid.org/0000-0001-5623-2968

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