



Optimizing 5-aminosalicylate for moderate ulcerative colitis: expert recommendations from the Asia-Pacific, Middle East, and Africa Inflammatory Bowel Disease Coalition

Filiz Akyüz¹, Yoon Kyo An², Jakob Begun², Satimai Aniwan³, Huu Hoang Bui⁴, Webber Chan⁵, Chang Hwan Choi⁶, Nazeer Chopdat⁷, Susan J Connor^{8,9}, Devendra Desai¹⁰, Emma Flanagan¹¹, Taku Kobayashi¹², Allen Yu-Hung Lai^{13,14}, Rupert W Leong¹⁵, Alex Hwong-Ruey Leow¹⁶, Wai Keung Leung¹⁷, Julajak Limsrivilai¹⁸, Virly Nanda Muzellina^{19,20}, Kiran Peddi²¹, Zhihua Ran²², Shu Chen Wei²³, Jose Sollano²⁴, Michelle Mui Hian Teo¹⁴, Kaichun Wu²⁵, Byong Duk Ye²⁶, Choon Jin Ooi²⁷

¹Department of Gastroenterology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye; ²Department of Gastroenterology, Mater Hospital Brisbane, Brisbane, Australia; ³Division of Gastroenterology, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand; ⁴Department of Gastroenterology, University Medical Center, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam; ⁵The Gastroenterology Group, Gleneagles Hospital, Singapore; ⁶Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea; ⁷Department of Gastroenterology, Baragwanath Hospital, University of the Witwatersrand, Johannesburg, South Africa; ⁸Department of Gastroenterology, Liverpool Hospital, Sydney, Australia; ⁹South Western Clinical School, University of New South Wales, Sydney, Australia; ¹⁰Division of Medical Gastroenterology, P. D. Hinduja Hospital, Mumbai, India; ¹¹Department of Gastroenterology, St. Vincent's Hospital, Melbourne, Australia; ¹²Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan; ¹³Global Health Program, College of Public Health, National Taiwan University, Taipei, Taiwan; ¹⁴Ferring Pharmaceuticals, Singapore; ¹⁵Department of Gastroenterology, Concord Hospital, Sydney, Australia; ¹⁶Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; ¹⁷Department of Medicine, University of Hong Kong, Hong Kong, China; ¹⁸Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; ¹⁹Gastrointestinal Endoscopy Center, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; ²⁰Universitas Indonesia, Jakarta, Indonesia; ²¹Department of Gastroenterology, Yashoda Hospital, Hyderabad, India; ²²Department of Gastroenterology, Zhoupu Hospital, Shanghai University of Medicine & Health Sciences, Shanghai, China; ²³Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; ²⁴Faculty of Medicine and Surgery, University of Santo Tomas, Manila, Philippines; ²⁵Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, China; ²⁶Department of Gastroenterology and Inflammatory Bowel Disease Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; ²⁷Duke-NUS Medical School, Singapore

The lack of clear definition and classification for “moderate ulcerative colitis (UC)” creates ambiguity regarding the suitability of step-up versus top-down treatment approaches. In this paper, experts address crucial gaps in assessing and managing moderate UC. The Asia-Pacific, Middle East, and Africa Inflammatory Bowel Disease Coalition comprised 24 experts who convened to share, discuss and vote electronically on management recommendations for moderate UC. Experts emphasized that the goal of treating UC is to attain clinical, biomarker, and endoscopic remission using cost-effective strategies such as 5-aminosalicylates (5-ASAs), well-tolerated therapy that can be optimized to improve outcomes. Experts agreed that 5-ASA therapy could be optimized by maximizing dosage (4 g/day for induction of remission), combining oral and topical administration, extending treatment duration beyond 8 weeks, and enhancing patient adherence through personalized counselling and reduced pill burden. Treatment escalation should ideally be reserved for patients with predictors of aggressive disease or those who do not respond to 5-ASA optimization. Premature treatment escalation to advanced therapies (including biologics and oral small molecules) may have long-term health and financial consequences. This paper provides consensus-based expert recommendations and a treatment algorithm, based on current evidence and practices, to assist decision-making in real-world settings. (Intest Res 2025;23:37-55)

Key Words: Ulcerative colitis; 5-Aminosalicylates; Treatment optimization; Inflammatory bowel diseases

Received June 18, 2024. Revised August 8, 2024. Accepted August 9, 2024.

Correspondence to Choon Jin Ooi, Duke-NUS Medical School and Gleneagles Medical Centre, 6 Napier Road, #10-02 Singapore 258499, Singapore. Tel: +65-6471-2500, Fax: +65-6471-2578, E-mail: eddyooi@duke-nus.edu.sg

INTRODUCTION

Ulcerative colitis (UC) is a chronic bowel disease characterized by inflammation of the colon and/or rectum,^{1,2} and also by genotypic and phenotypic heterogeneity, which present a clinical challenge for categorization and subsequent treatment decision-making.³⁻⁵ Existing guidelines offer recommendations for the management of “mild-to-moderate” or “moderate-to-severe” UC.^{1,2,6} Mild-to-moderate disease management begins with conventional therapies such as 5-aminosalicylates (5-ASAs), with a sequential step-up approach with corticosteroids employed if initial therapy fails. Conversely, an early treatment escalation approach is typically preferred in moderate-to-severe UC, involving advanced therapies (biologics and/or oral small molecules) for induction of remission, followed by the potential for de-escalation to conventional management after remission is attained.^{1,2,6,7}

Population-based studies have reported that the majority of adult patients have mild-to-moderate disease at the time of diagnosis and subsequent years.^{8,9} There is a notable gap in the categorization of UC activity, as there is heterogeneity in defining what constitutes “mild-to-moderate” UC in clinical trials: Earlier 5-ASA studies aligned with the Truelove and Witts criteria,^{10,11} while relatively recent studies of biologics also take into consideration endoscopic findings, through use of tools such as the Mayo Endoscopic Subscore (MES).¹²⁻¹⁴ Furthermore, there is a lack of precise clinical practice guidelines concerning the definition and optimal management of “moderate” UC as an independent condition, representing a grey area in the field where the step-up and top-down approaches converge. Consequently, patients with moderate UC may be at risk of receiving either suboptimal treatment or overtreatment.

Conventional therapies such as 5-ASAs are considered the gold standard for first-line treatment of mild-to-moderate UC.^{1,2,6} A meta-analysis has demonstrated that oral prolonged-release 5-ASA, in particular, is effective for inducing remission in patients with moderately active UC.¹⁵ However, 5-ASAs may be underutilized in moderate UC, owing to an emerging trend favoring the top-down approach; early initiation of advanced therapies is driven by the perception that conventional therapies may not be sufficient in this space.¹⁶⁻¹⁸ However, there are limited data to support early escalation in UC, and potential risks should be considered alongside any perceived benefit of this treatment strategy.¹⁶ Before escalating to advanced therapies, physicians must take into account a range of healthcare

and cost-related considerations, encompassing the identification of suitable patients through screenings for latent infections, conducting baseline laboratory tests and assessments, verification of up-to-date vaccination status, and the provision of comprehensive counseling regarding advanced therapies prior to treatment initiation.¹⁹⁻²¹ Despite these considerations, early escalation to advanced therapies may not benefit every patient and may even be unnecessary in some cases.¹⁶

Of greater concern are the long-term health and financial consequences of premature treatment escalation beyond 5-ASA. Chronic use (≥ 3 months) of oral corticosteroids have been shown to elevate the risk of infection among patients with inflammatory bowel disease (IBD),²² limiting the use of such agents within the Asia-Pacific region where infectious diseases such as tuberculosis and hepatitis B are endemic and latent infection is prevalent.^{21,23-25} Accordingly, the health impacts of premature use of antagonists of tumor necrosis factor α (anti-TNFs) are also a concern. A 5-year observational study of 2,239 individuals found that anti-TNFs pose significantly greater risk of severe infection compared with conventional therapy such as immunosuppressants.²⁶

Patients may also face significant healthcare expenses with the early and long-term use of advanced therapies, primarily in the absence of sufficient reimbursement policies or insurance coverage. Expenses may encompass out-of-pocket costs for advanced therapies, clinic visits, screening tests, and infection prophylaxis measures.^{20,27} In East Asia, the public health system typically covers or provides financial assistance for conventional treatments such as 5-ASAs, corticosteroids, and immunomodulators, while stringent reimbursement policies are often in effect for advanced therapies. Consequently, patients may incur high expenses associated with advanced therapies.^{21,27,28}

In conjunction with the use of advanced therapies such as biologics, reactive therapeutic drug monitoring is conditionally recommended to guide treatment changes,²⁹ but such monitoring may not be available, financially accessible, or convenient for patients.³⁰ Furthermore, the recommended target trough levels for advanced therapies may vary by study and be largely based on research conducted on non-Asian populations. Ethnic variability may impact the pharmacokinetics and pharmacodynamics of advanced therapies; thus it is necessary to validate the target drug levels through local or regional clinical trials.²⁰ Furthermore, certain individuals may not respond to biologics and/or small molecules, leading to an early exhaustion of available treatment choices as the disease ad-

vances.³¹ Patients may also eventually experience a loss of response to individual biologics, necessitating treatment switch³²; one study found that 39% of patients receiving vedolizumab experienced loss of response within a 12-month treat-

ment period.³³ Given these numerous considerations, the decision to escalate to advanced therapies is not one that may be taken lightly.

Table 1. Summary of Recommendations for the Management of Moderate UC

No.	Recommendation and proportion of expert agreement
1	Moderate UC is a unique phenotype of UC and warrants clinical attention (100%).
2	The lack of timely and accurate risk stratification for patients may lead to consequences such as: (1) Suboptimal treatment (95%) or a delay in treatment initiation or treatment escalation (89%) if the disease activity is underestimated; (2) An increased risk of colectomy or hospitalization due to undertreated disease activity (58%); (3) The overuse of healthcare resources if the treatment does not adequately address disease activity or if biologics are prematurely administered (26%); (4) Reduced treatment adherence if the medication is perceived by patients to be ineffective for controlling symptoms (21%).
3	Truelove and Witts criteria may be employed for identifying patients with moderate UC (50%).
4	Ambiguous treatment pathways for moderate UC may lead to: (1) Early and long-term exposure to adverse effects of advanced therapies (83%); (2) Early and long-term costs of biologics (72%); (3) Treatment fatigue for patients (44%); (4) Early exhaustion of biologics options due to loss of response (33%).
5	The anticipated timeframe for an initial clinical response to induction treatment with 5-ASAs in patients with moderate UC is between 2 and 4 weeks (78%).
6	Early age at diagnosis, extensive colitis, and frequent flares requiring steroid treatment or hospitalization are indicators of a more aggressive form of moderate UC (100%).
7	Other indicators of a more aggressive form of moderate UC include male gender, being a smoker, concurrent primary sclerosing cholangitis or other EIMs, and moderate endoscopic activity (56%).
8	Oral corticosteroids to 5-ASA therapy should not be added to a treatment regimen based solely on the presence of one or more accepted predictors of aggressive disease, because each predictor may be weighted differently according to their distinct HRs for aggressive disease (67%).
9	The optimal oral ASA dose for induction of remission in moderate UC is 4 g/day (81%).
10	Topical administration of ≥ 1 g/day 5-ASA is recommended for inducing remission in patients with distal moderate UC, inclusive of proctosigmoiditis and proctitis (82%).
11	The definition of "inadequate response" to 5-ASAs for moderate UC as a failure to attain a reduction $\geq 50\%$ in rectal bleeding and stool frequency (94%).
12	Risk factors that contribute to "inadequate response" to 5-ASA include: (1) Frequent symptom flares requiring corticosteroids or hospitalization (89%); (2) Extensive colitis (67%); (3) Moderate endoscopic activity (39%); (4) Young age at diagnosis (33%); (5) Concurrent PSC or other EIM (17%); (6) Smoking (11%); (7) Male gender (6%).
13	In the absence of a response to 5-ASA therapy, either add-on oral budesonide MMX (9 mg/day) or corticosteroid (≥ 40 mg/day) should be used as an escalation strategy for induction of remission in moderate UC before immunomodulators or advanced therapies are considered (72%).
14	The definition of relapse is recurrence of disease symptoms, including failure to achieve rectal bleeding = 0, stool frequency = 0 or MES < 3 after 12 weeks of treatment, an adaptation of STRIDE-II recommendations (92%).

Twenty-four experts participated in voting.

UC, ulcerative colitis; 5-ASA, 5-aminosalicylates; EIM, extraintestinal manifestation; HR, hazard ratios; MMX, multimatrix; MES, Mayo Endoscopic Subscore; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease.

METHODS

On October 27, 2023, 24 members of the Asia-Pacific, Middle East, and Africa (APMA) IBD Coalition convened in Taiwan to address critical issues and ongoing challenges in the management of moderate UC in the APMA region. The APMA IBD Coalition consists of 24 experts from countries/regions such as Australia, China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, the Philippines, Singapore, South Africa, Taiwan, Thailand, Turkey, and Vietnam. The panel discussed and provided insights on the following objectives: (1) to define and establish a clinically relevant and practical approach to risk stratifying and managing moderate UC; (2) to employ a proactive approach to treating moderate UC based on region-specific predictive factors; (3) to review the current moderate UC management strategies to minimize the burden on both patients and healthcare; (4) to optimize the utilization of conventional therapies through improved treatment intensifica-

tion, dosage optimization, and treatment adherence before considering treatment escalation; and (5) to formulate cost-effective treatment strategies tailored to the APMA region. The discussions were followed by electronic live polling to quantify agreement on clinical approaches for moderate UC classification and treatment. The ensuing expert recommendations are presented herein and summarized in Table 1.

EXPERT RECOMMENDATIONS

1. Assessing Moderate UC

The APMA IBD Coalition members reached a unanimous consensus (100%) that moderate UC is a unique phenotype of UC and warrants clinical attention. A proportion of the coalition further indicated that the lack of timely and accurate risk stratification for patients may lead to consequences such as (1) suboptimal treatment (95%) or a delay in treatment initiation or treatment escalation (89%) if the disease activity is un-

Table 2. Comparison of Tools for UC Classification or Disease-Activity Assessment

	Truelove and Witts ^{37,42}	SCCAI ^{34,35}	MCS/MES ³⁵⁻³⁷	PGA ^{38,39}	UCEIS ^{40,41}
Variables	- Frequency of bowel movements - Rectal bleeding - Fever - Tachycardia - Anemia - ESR - CRP	- Number of stools (day and night) - Urgency of defecation - Blood in stool - General well-being - Extracolonic features	- Stool frequency - Rectal bleeding - Findings of flexible proctosigmoidoscopy - Physician's global assessment	- Stool frequency - Rectal bleeding - Sigmoidoscopy (assessed by contact friability test)	Endoscopic findings: - Vascular pattern - Extent of bleeding - Presence of erosions or ulcers
		Score range: 0–19	Score range: 0–12	Scale range: 0–3	Scale range: 0–8
Definition of mild-to-moderate UC	≤ 6 bloody stool frequency per day, no fever (temperature ≤ 37.8°C), no tachycardia (pulse ≤ 90 beats/min), no severe anemia (Hb ≥ 10.5 g/dL), ESR < 30 mm/hr, and CRP ≤ 30 mg/dL ⁴³	3–11 points ³⁵	MCS 3–10, rectal bleeding subscore ≥ 1, and MES score ≥ 2 ³⁵	1–2 points ^{38,39}	2–6 points ⁴¹
Definition of moderate UC	4 to 6 bloody stool frequency/day, no fever (temperature ≤ 37.8°C), no tachycardia (pulse ≤ 90 beats/min), no severe anemia (Hb ≥ 10.5 g/dL), low ESR (< 30 mm/hr), and CRP ≤ 30 mg/dL ⁴³	6–11 points ³⁵	MCS score 6–10 points ³⁵	2 points, with a score of ≥ 1 point in both the stool frequency and rectal bleeding clinical assessments and a score of ≥ 2 points in the sigmoidoscopy assessment with a positive friability assessment ^{38,39}	5–6 points ⁴¹

UC, ulcerative colitis; SCCAI, Simple Clinical Colitis Activity Index; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Subscore; PGA, Physician's Global Assessment; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin.

derestimated; (2) an increased risk of colectomy or hospitalization due to undertreated disease activity (58%); (3) the overuse of healthcare resources if the treatment does not adequately address disease activity or if biologics are prematurely administered (26%); and (4) reduced treatment adherence if the medication is perceived by patients to be ineffective for controlling symptoms (21%). The heterogeneity in clinical presentations between patients presents a key barrier to establishing a precise definition for moderate UC. It is imperative to establish a clear definition and set of criteria for assessing moderate UC, to ensure timely selection and optimization of appropriate treatment strategies.

UC is currently assessed by a range of measures, including clinical symptoms, laboratory studies, and endoscopic assessment. Some of the most commonly used tools in UC include the Truelove and Witts criteria,^{10,11} Simple Clinical Colitis Activity Index (SCCAI),^{34,35} the Mayo Clinic Score and its modification,³⁵⁻³⁷ the Physician's Global Assessment,^{38,39} the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (Table 2).^{40,41}

Half of the expert panel (50%) indicated that they employed the Truelove and Witts criteria for identifying patients with moderate UC, while the other experts stated that these criteria may be overly restrictive, considering case heterogeneity, and are currently lacking validation. Additionally, patients must undergo blood tests, assessing C-reactive protein, erythrocyte sedimentation rate and hemoglobin, to determine whether they fulfill the Truelove and Witts criteria for moderate UC.^{42,43} The Truelove and Witts criteria are considered more useful for diagnosing acute severe UC than moderate UC, and in the hospitalization setting. Comparatively, the SCCAI could capture nuanced aspects of the disease state, e.g., by considering urgency and nocturnal bowel movements,³⁴ while some countries require MES information for treatment reimbursement. However, for SCCAI and Mayo scores, there may be interobserver variations for physician's assessment.³⁵

Currently, there is no single tool that has been universally acknowledged and adopted as the "standard" index for classifying moderate UC.^{37,44-46} However, evaluating the clinical manifestation of UC is of utmost importance, encompassing factors such as stool frequency and volume, urgency, bleeding, nocturnal symptoms, body mass index, and weight loss, as well as the subjective experiences reported by patients. Furthermore, it is imperative to consider individual patient variables, such as the reduced hemoglobin levels in females who are menstruating. There remains a need for a well-accepted, uniform, validated, simple and practical clinical index

that considers clinical presentation, patient-reported symptoms, and objective/laboratory criteria.

2. Treatment of Moderate UC: Challenges and Unmet Needs

The APMA IBD Coalition outlined key challenges to the appropriate treatment of moderate UC, including a lack of clear treatment recommendations leading to delayed intervention, particularly among gastroenterologists with limited exposure to UC in practice. In the APMA region, variations in treatment accessibility, affordability, reimbursement policies, and eligibility criteria hinder a universal approach to moderate UC.^{21,28} The panel indicated that ambiguous treatment pathways for moderate UC may lead to (1) early and long-term exposure to adverse effects of advanced therapies (83%)^{20,21,26,47}; (2) early and long-term costs of biologics (72%)^{21,28}; (3) treatment fatigue for patients (44%)⁴⁸; and (4) early exhaustion of biologics options due to loss of response (33%), as described earlier.^{32,33}

The experts emphasized the need to establish a treatment pathway for moderate UC that provides clear guidance on (1) the selection of induction treatment, including dosage and duration, and administration route based on the location and extent of disease; (2) risk stratifying strategies to identify the need to escalate therapy; and (3) de-escalation strategies upon achievement of remission. However, such treatment guidelines must also account for patient heterogeneity in terms of treatment history, clinical presentation, disease progression and treatment response.

1) Treatment Goals in Moderate UC

Establishing clear treatment goals is essential for tailoring interventions to the specific needs of individuals with moderate UC. These goals aid in timely decision-making for when to escalate or de-escalate interventions and further aid in determining optimal therapy duration. The International Organization for the Study of Inflammatory Bowel Diseases implemented the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-II initiative, which incorporated a treat-to-target approach. The STRIDE-II algorithm indicates that the key short-, medium, and long-term targets for UC treatment in adults include, respectively, (1) achieving a clinical response (decrease of at least 50% in patient-reported outcome 2 [PRO2; rectal bleeding and stool frequency]); (2) clinical remission (PRO2 [rectal bleeding=0 and stool frequency=0] or partial Mayo [<3 and no individual item score >1]) or normalizing both C-reactive protein to values under the upper limit of nor-

Table 3. Treatment Targets for Moderate Ulcerative Colitis as Recommended by the APMA IBD Coalition

Short term (2–8 weeks)	Medium term (8–12 weeks)	Long term (> 12 weeks)
▪ Clinical response^a within 2 weeks ▪ Clinical remission within 4–8 weeks	▪ Normalizing CRP ▪ Reduction in FC	▪ Improvement in quality of life ▪ Endoscopic remission ▪ Histologic remission ▪ Resolution of disability ▪ Normalization of growth velocity in pediatrics ▪ Avoidance of long-term corticosteroids, colorectal cancer development and proctocolectomy

^aAssessed through a combination of clinical symptoms± improvement in CRP levels and/or ultrasound response.

APMA IBD Coalition, Asia-Pacific, Middle East, and Africa Inflammatory Bowel Disease Coalition; CRP, C-reactive protein; FC, fecal calprotectin.

mal and fecal calprotectin to 100–250 µg/g; and (3) endoscopic remission (either an MES of 0 points or UCEIS ≤ 1 point).⁴⁹ Aligned with the STRIDE-II recommendations, the APMA IBD Coalition members indicated their preferred and specific treatment targets for moderate UC and the expected time to achieve these short-, medium-, and long-term goals, as outlined in Table 3. The anticipated timeframe for an initial clinical response to induction treatment with 5-ASAs in patients with moderate UC is reported to be between 2 and 4 weeks, as reported by 78% of the experts.

There are numerous benefits to setting and achieving treatment goals. For example, patients who attain mucosal healing exhibit (1) lower rates of clinical relapse (18% with MES 0 vs. 30% with MES 1: odds ratio [OR], 0.42; 95% confidence interval [CI], 0.29–0.62; $P < 0.00001$)⁵⁰; (2) reduced hospitalization risk (OR, 0.23; 95% CI, 0.04–1.35; $P = 0.10$)⁵⁰; (3) higher health-related quality of life (HRQoL) ($P < 0.001$)^{51,52}; (4) fewer surgeries (relative risk [RR], 0.28; 95% CI, 0.17–0.46; $P < 0.001$)⁵³; and (5) higher rates of corticosteroid-free remission (RR, 2.07; 95% CI, 1.27–3.36; $P = 0.003$).⁵³ Achieving histological remission is associated with increased odds of relapse-free survival,⁵⁴ a predicted decrease in corticosteroid usage, and a lower occurrence of acute severe colitis requiring hospitalization, compared with even endoscopic remission.⁵⁵ Overall, individuals with UC who succeed in achieving remission demonstrate less risk of hospitalization and surgery, as well as a lower associated direct healthcare resource utilization cost than those with active disease.⁵⁶ On the other hand, suboptimal treatment or overtreatment in UC management imposes a substantial economic burden. Individuals with active UC may exhibit impaired work productivity and activity compared with those in clinical remission.⁵⁷ The APMA IBD Coalition concluded that, ultimately, the goal of treating UC is to attain clinical,

biomarker, and endoscopic remission using cost-effective strategies.

2) 5-ASA Safety and Efficacy for Mild-to-Moderate UC

International and regional guidelines recommend 5-ASAs for first-line therapy for mild-to-moderate UC.^{1,2,6,58-60} Accordingly, up to 88%–97% of patients with UC receive 5-ASAs within 1 year of diagnosis in practice.⁶¹⁻⁶³ Major guidelines recommend the use of an oral 5-ASA at ≥ 2 g/day for induction and maintenance of remission in UC patients with mild-to-moderate UC.^{1,2,6} A combination of oral 5-ASA and topical (rectal) 5-ASA is recommended for those who have suboptimal response to one form alone, and for patients with left or extensive UC.^{1,2,6}

The efficacy of 5-ASA for the induction and maintenance of remission in mild-to-moderate UC has been evaluated in multiple trials.⁶⁴ A meta-analysis of UC randomized controlled trials (RCTs) reported that 5-ASA generally outperformed corticosteroids in inducing histologic remission,⁶⁵ while another meta-analysis demonstrated that 2–12 weeks of treatment with 5-ASA resulted in mucosal healing in approximately 50% of patients with UC.⁶⁶ Mucosal healing rates were reported as high as 56% and 50% after induction with topical or oral 5-ASAs, respectively.⁶⁷ With 12 months of maintenance therapy, the rate of mucosal healing was reported to be 85.4% and 81.4%, respectively, in patients who received prolonged-release 5-ASA at doses of 2 g once daily or 1 g twice daily.⁶⁸ A systematic review of 11 RCTs reported that predictors for good response to 5-ASA and budesonide include mild or moderate disease activity, no extraintestinal manifestation (EIM), previous treatment with corticosteroids, shorter disease duration (< 5 years), and distal disease.³⁷

The safety profile of 5-ASA is well-established.^{15,69,70} Although the administration of 5-ASA agents has been occasionally as-

sociated with adverse effects such as headache, nausea, and nasopharyngitis, symptomatic management may suffice, and discontinuation of 5-ASA is not required in every instance.⁷⁰

3) Treatment of Moderate UC: Predictors of Aggressive

Disease for Early Escalation

Physicians must consider an accelerated step-up treatment approach for patients who exhibit key predictors of aggressive disease that may not be adequately controlled with a standard 5-ASA regimen. The significance of predicting treatment response is being increasingly recognized in the context of personalized and preventive healthcare, underscoring the shift from a reactive to a proactive approach.

The first step involves the identification of patients with moderate UC who would benefit from an early escalation strategy owing to disease factors or risk of poor treatment outcomes.⁴⁷ Le Berre et al.⁴⁵ proposed various factors that could serve as predictors for aggressive disease potentially requiring the implementation of advanced therapeutic intervention; these include an early age of diagnosis, male gender, extensive colitis, frequent flares requiring the use of corticosteroids or hospitalization, being a smoker, concurrent primary sclerosing cholangitis (PSC) or other EIMs, and exhibiting moderate endoscopic activity.⁴⁵ However, in the discussion regarding these criteria, only 56% of the APMA IBD Coalition accepted all aforementioned predictors of aggressive disease. The panel agreed that early age at diagnosis, extensive colitis, and frequent flares requiring steroid treatment or hospitalization are accepted indicators of a more aggressive form of the disease. Owing to lack of clinical evidence, the experts were less convinced of the predictive value of other factors.

Overall, 67% of the experts indicated they would not add oral corticosteroids to 5-ASA therapy based solely on the presence of one or more accepted predictors of aggressive disease, because each predictor may be weighted differently according to their distinct hazard ratios (HRs) for aggressive disease. However, should a treating physician be convinced of the presence of aggressive disease based on specific indicators (i.e., young age at UC diagnosis, extensive colitis, and frequent flares requiring steroid treatment or hospitalization), experts recommend that oral corticosteroids at 30–40 mg/day be added alongside the oral 5-ASA regimen for induction of remission of moderate UC. If the disease is refractory to oral corticosteroids, then immunomodulators such as thiopurine or advanced therapies such as anti-TNF, anti-integrin, anti-interleukin 12/23, Janus kinase inhibitor, or sphingosine-1 phos-

phate receptor modulator should be considered as second-line treatment.^{1,71}

3. Treatment of Moderate UC: Optimization of 5-ASA for Patients with Moderate UC

Current guidelines recommend conventional 5-ASAs as induction therapy for remission in patients with mild-to-moderate UC, followed by advanced therapies if conventional therapies are no longer effective.^{1,2,59,60} Before a treatment is considered “ineffective,” the physician should first ensure that the treatment has been correctly and fully utilized at the maximum dose and optimum duration.¹⁷ Ultimately, these measures to improve the utilization of conventional medicines for moderate UC may effectively conserve the use of advanced therapies for patients experiencing severe UC.^{17,45}

The optimization of 5-ASA therapy can be achieved by implementing measures suggested by the APMA IBD Coalition, which have been modified based on strategies proposed in previous literature^{17,45}: maximizing 5-ASA dosage, incorporating topical therapy, enhancing patient adherence through education and by streamlining the dosing strategy and delivery, and prolonging treatment duration.

1) Maximizing the 5-ASA Dose

For patients with moderate UC, a high/optimized-dose 5-ASA should be considered as the first-line option for induction of remission.⁴⁵ The definition of “high-dose” 5-ASA may differ based on product, but it is generally defined as ≥ 3 g/day. A systematic review and meta-analysis of 40 RCTs revealed that oral 5-ASA at ≥ 3.3 g/day was significantly more effective than lower doses at inducing remission.⁶⁴ However, real-world data indicate that up to 37% of patients with UC were taking 5-ASA doses of ≤ 2.4 g daily before they were switched to an immunosuppressive drug⁷²; suggesting that dose maximization is not sufficiently or uniformly practiced among clinics.

In total, 81% of the experts agreed that 4 g/day is the optimal oral dose for remission induction in moderate UC. This statement was supported by a multicenter, randomized, double-blind, parallel-group clinical trial, which found that 4 g/day 5-ASA significantly outperformed 2.25 g/day in improving the UC-disease activity index (DAI) score in moderately active UC, while the 2 doses exhibited comparable safety profiles.⁷³ In the IMPACT study, patients with mild-to-moderate UC receiving higher induction doses of oral prolonged-release 5-ASAs (≥ 4 g/day) had a significantly lower risk of recurrence than those who received a lower induction dose of 2 to < 4 g/

day (26.6% vs. 62.5%, $P=0.04$).⁷⁴ Similarly, the real-world Quartz study demonstrated that 4 g/day prolonged-release 5-ASA treatment in patients with mild-to-moderate ulcerative proctitis and proctosigmoiditis, used alone or in combination with a rectal formulation, led to significant improvement in patient HRQoL, which was found to be proportionally related to disease activity.⁷⁵ In a study evaluating the effects of an 8-week treatment regimen of 4 g/day once-daily 5-ASA in patients with mild-to-moderate UC, it was observed that 52.1% of the participants achieved endoscopic remission, 92.0% reported enhancements in their UC-DAI score, and 87.5% attained mucosal healing. The median duration to remission was determined to be 26 days.⁷⁶

An oral 5-ASA dose higher than 4 g/day may not be required. Bayesian meta-analysis data have shown that 4 g/day oral prolonged-release 5-ASA is as effective as 4.8 g/day multi-matrix (MMX) 5-ASA for inducing clinical and endoscopic remission in 8 weeks in patients with moderately active UC. Similarly, in terms of achieving composite remission in 8 weeks, a second analysis comparing oral prolonged-release 5-ASA at 4 g/day and Eudragit S-coated 5-ASA at 4.8 g/day found no significant difference between the treatments.¹⁵ It should be noted that commercially available 5-ASAs differ in their formulations, release mechanisms, and targeted regions within the gastrointestinal tract. Understanding these distinctions is critical for tailoring IBD treatment to the specific needs of individual patients.

The majority (82%) of the APMA IBD Coalition agreed that topical administration of ≥ 1 g/day 5-ASA is recommended for inducing remission in patients with distal moderate UC, inclusive of proctosigmoiditis and proctitis. This statement aligns with current guidelines, which strongly recommend 1 g 5-ASA suppositories as first-line treatment for mild-to-moderate proctitis, owing to the higher mucosal concentrations achieved with topical administration versus oral administration of 5-ASA.^{1,58,77} The APMA IBD Coalition recommends that a topical dose be individualized based on patient symptoms, patient tolerability, desired outcomes, and response. Some patients may benefit from a higher dose than 1 g/day, while others may require more than one form of topical treatment depending on the location of UC lesions, e.g., a combination of enema and suppository may be necessary to achieve optimal therapeutic outcomes. Patients with proctitis who are not responding adequately to suppositories may benefit from the early addition of oral 5-ASA,⁵⁸ such as prolonged-release 5-ASAs that can provide extensive coverage of actively inflamed colonic mucosa.⁷⁸

2) Using Topical Therapy in Combination with Oral 5-ASA

A decision tree analysis assessing 10,000 recently diagnosed patients with mild to moderately active UC throughout induction and 1 year of maintenance therapy revealed that optimizing 5-ASA treatment, via a combination of oral and rectal 5-ASA regimen and maximizing the dose, offers both cost-effective and clinical advantages, supporting broader integration of optimization into clinical settings.¹⁸ However, topical treatments may be underutilized in UC.⁷⁹

Evidence indicates that for patients who are not adequately responding to induction with oral 5-ASA alone, adding topical 5-ASA can substantially improve remission rates in active UC.^{1,2,6,17,64} A systematic review of 48 RCTs showed that in patients with mildly to moderately active left-sided or extensive UC, combined oral and topical 5-ASA therapy and high-dose 5-ASA (> 3 g/day) are superior to standard-dose oral 5-ASA (2–3 g/day) for induction of clinical and endoscopic remission.⁸⁰ Additionally, the PINCE study showed that 8 weeks of oral 5-ASA 4 g/day plus 4 weeks of 1 g/day 5-ASA enema led to a higher rate of remission than oral 5-ASA combined with placebo enema in patients with extensive mildly to moderately active UC (64% vs. 43%, $P=0.030$).⁸¹ The combination of a 5-ASA enema with oral prolonged-release 5-ASA 4 g once daily for 8 weeks has been found to be well tolerated and effective for inducing clinical and endoscopic remission in patients with mildly to moderately active UC.⁷⁶

An alternative to a topical 5-ASA are add-on topical corticosteroids, which may be better tolerated by some patients. However, a meta-analysis of 18 studies showed that topical 5-ASA may induce higher rates of remission than topical corticosteroids in patients with ulcerative proctitis.⁸² Indeed, guidelines suggest that rectal corticosteroids be reserved for patients with proctosigmoiditis or proctitis who are intolerant of, or refractory to, topical 5-ASA.^{1,58}

3) Extending Treatment Duration

Although clinical response is typically assessed 2 weeks after initiation of an induction regimen, not all patients may exhibit a complete response within the timeframe. The APMA IBD Coalition recommends that if a patient displays some level of improvement during induction, the 5-ASA regimen could be continued beyond 8 weeks until the desired outcomes are attained. According to the expert panel, patients can be maintained indefinitely on 5-ASAs if they continue to respond well to the treatment. In a multicenter retrospective study including patients receiving induction therapy with 4.0 g/day 5-ASA,

prolonged treatment (> 105 days) was shown to lead to a lower relapse rate (29.8%) than short-term treatment (48.3%) ($P < 0.05$).⁸³ Another study including patients with mild-to-moderate UC who received oral prolonged-release 5-ASA found that extended duration of treatment was significantly correlated with a decreased risk of recurrence (> 6 months vs. 3–6 months: HR, 0.19; 95% CI, 0.08–0.46; $P < 0.05$). This was particularly relevant for individuals administered with high-dose (≥ 4 g/day) 5-ASA (HR, 0.15; 95% CI, 0.06–0.40) compared with those who received 2 to < 4 g/day (HR, 0.26; 95% CI, 0.01–11.9).⁷⁴

In patients with UC who demonstrate a high level of adherence to the prescribed medication, exhibit mild clinical progression of the disease, possess low levels of fecal calprotectin, and/or achieve complete healing of the mucosal lining, it may be appropriate to reduce the maintenance dose of 5-ASA.^{84,85} However, the APMA IBD Coalition stressed that patients with moderate UC should not be de-escalated from 5-ASA completely, in order to maintain disease control.

4) Improving Patient Adherence

Previous studies have shown that patient adherence to treatment is poor, from as little as 19% to a maximum of 60% adherence.⁸⁶⁻⁸⁹ There are many potential reasons for non-adherence to UC treatment, including a high pill burden or frequency of administration, financial constraints, disease denial, low levels of education, concerns about drug-food interactions, forgetfulness, unclear medication regimens, no perceived effect of medication, patient-led treatment cessation if symptoms resolve, and non-availability of medication.⁹⁰⁻⁹² Non-adherence was shown to be associated with approximately 5 times increased risk of disease recurrence,^{93,94} while adherence to medication is linked to a decrease in disability related to IBD.⁹⁵ Thus, optimizing adherence to 5-ASA is a critical goal in clinical practice.

Adherence could be improved by reducing pill burden and frequency (from twice daily to once daily) or switching to oral formulations other than tablets (e.g., granules).^{45,96} Additionally, treatment acceptability may be improved by selecting a 5-ASA option that has been demonstrated to have fewer food-drug interactions and is therefore not considerably impacted by mealtimes.⁷⁸

An RCT conducted in patients with quiescent UC showed that those who received prolonged-release oral 5-ASA 2 g once daily had improved remission rates, acceptability, and self-reported adherence to therapy than those who received oral 5-ASA 1 g twice daily. At year 1, the study found that 70.9% of

patients who received a daily dose of 2 g 5-ASA maintained remission, while only 58.9% of patients who received a twice-daily dose of 1 g 5-ASA achieved the same outcome ($P = 0.024$).⁹⁷ Furthermore, the PODIUM trial showed that prolonged-release 5-ASA at once-daily 2 g is similarly effective to the standard twice-daily 5-ASA at 1 g/day for the maintenance of remission in mild-to-moderate disease among patients with left-sided UC.⁶⁸ According to a cost-utility analysis performed from the perspective of the UK National Health Service, administering 2 g 5-ASA once daily to maintain remission of UC was more cost-effective than administering 1 g twice daily.⁹⁸

A multifaceted approach is needed to encourage patient adherence, involving professional support, education, and a clear explanation/rationale for treatment optimization, coupled with encouragement and an ongoing patient-centric dialogue during consultations. In childbearing-aged women, dedicated IBD education is associated with increased medication adherence and improvement in pregnancy-specific knowledge.^{95,99}

Experts agreed that pharmacists, IBD nurses, and clinical research staff play an important role in ensuring patient adherence to therapy. Clinic nurses in particular are crucial for educating patients about the pathophysiology of UC, the treatment plan, and the importance of adherence for disease control; they may also assist in ongoing monitoring to ensure optimal patient adherence. Responsibility for implementing adherence strategies may also be assumed by gastroenterologists when clinic nurses are unavailable.

Patient empowerment and technological advances may aid in improving adherence. Implementing accessible tools, such as a visual analog scale or web-based adherence questionnaires to be completed before consultation, can enhance the monitoring of adherence to treatment plans in patients with UC.¹⁰⁰⁻¹⁰² With patient consent, automated or personalized communication via messaging platforms can also serve as reminders to maintain adherence to medication in the time between consultations. Medication non-adherence among individuals with IBD can be addressed with a single personalized counseling session conducted by an IBD pharmacist, the positive impact of which was shown to be sustained for a duration of 2 years, attributed to the improvement in medication acceptance.¹⁰³

5) Switching 5-ASAs

The experts agreed that switching between 5-ASA therapy formulations (e.g., from tablets to granules) can help improve ad-

herence, as discussed earlier. A study conducted in Japan, involving patients who initiated treatment with 5-ASA tablets and switched to 5-ASA granules, revealed that those who maintained treatment with 5-ASA granules exhibited a notable greater adherence (97.3%) than those who switched back to tablets (88.6%).¹⁰⁴ A second study highlighted that 5-ASA tablet was less acceptable to patients than a controlled-release formulation of 5-ASA in granule form (acceptability was 33% for the tablet vs. 76% for the granules, $P=0.0005$), and that the granule form may be marginally more suitable for long-term medication owing to numerically greater patient adherence (adherence rates were 91% for the tablet vs. 94% for the granules, $P=0.139$).¹⁰⁵

The experts stated that switching between 5-ASA tablet formulations alone is generally not successful, except in rare cases where the patient has an adverse reaction to non-active ingredients such as stabilizers or coatings. However, it is more likely that such patients will not tolerate 5-ASA in any other formulation. “5-ASA intolerance” is characterized by exacerbation of diarrhea, fever and abdominal pain.¹⁰⁶ The majority of literature pertaining to 5-ASA intolerance or “allergy” originates from Japan, with one study revealing that the condition may have a genetic component.¹⁰⁷ In other countries in the Asia-Pacific region, prevalence and potential causative factors are currently not well-documented. Rather than 5-ASA switching, guidelines recommend that 5-ASA intolerance be addressed through treatment escalation to thiopurines or advanced therapies.²

4. Treatment Escalation Beyond 5-ASA for Patients with Moderate UC

When all available options for optimizing 5-ASA treatment have been exhausted, escalating to immunomodulatory agents and/or advanced therapies may be considered,^{1,47} in alignment with guidelines that recommend escalation for patients with moderate-to-severe UC with inadequate response or intolerance to conventional therapy.² As per the STRIDE-II consensus recommendations, 94% of the APMA IBD Coalition would define “inadequate response” to 5-ASAs for moderate UC as a failure to attain a reduction $\geq 50\%$ in rectal bleeding and stool frequency.⁴⁹ Risk factors that were identified to contribute to “inadequate response” to 5-ASA include (1) frequent symptom flares requiring corticosteroids or hospitalization (89%); (2) extensive colitis (67%); (3) moderate endoscopic activity (39%); (4) young age at diagnosis (33%); (5) concurrent PSC or other EIM (17%); (6) smoking (11%); and (7) male gender (6%).

The majority (72%) of experts in the APMA IBD Coalition agreed that in the absence of a response to 5-ASA therapy, either add-on oral budesonide MMX (9 mg/day) or corticosteroid (≥ 40 mg/day) should be used as an escalation strategy for induction of remission in moderate UC before immunomodulators or advanced therapies are considered.¹⁰⁸ Budesonide MMX exhibits a favorable risk-benefit profile compared with oral corticosteroids in adult patients with IBD.¹⁰⁹⁻¹¹² The MMX formulation utilizes an outer coating that dissolves at pH > 7.0 , allowing the orally-administered drug to traverse and be distributed uniformly throughout the length of the colon.^{109,112} Budesonide is subject to extensive first-pass hepatic metabolism ($>90\%$), demonstrated to result in low systemic bioavailability.^{112,113} Consequently, budesonide MMX serves as a valuable tool to prevent overexposure to the systemic risks posed by oral corticosteroids.¹⁰⁹ Given the high burden of infectious disease in the Asia-Pacific region described earlier,²³⁻²⁵ this is a critical consideration in treatment decision-making.

Treatment escalation is also warranted in the event of relapse of moderate UC. As agreed by 92% of the experts, relapse is defined as recurrence of disease symptoms, including failure to achieve rectal bleeding=0, stool frequency=0 or MES < 3 after 12 weeks of treatment, an adaptation of STRIDE-II recommendations.⁴⁹ The clinical response to relapse should be assessed by taking into account critical factors such as the patient’s treatment history, the number of relapses in the previous year, and any recent stressful or traumatic life events. Such details may have a significant effect on decision-making; as such, robust history-taking is essential. For example, a relapse following an extended period of successful remission on 5-ASA might be precipitated by a singular stressful life event that may be self-limiting and therefore does not necessitate treatment escalation.

If the decision is made to escalate treatment for moderate UC, there may be benefit in continuing the 5-ASA treatment regimen as concomitant treatment, if tolerated by the patient, for the following reasons: (1) to assist in the management of symptoms, particularly those associated with distal inflammation, until patients demonstrate a response to advanced therapy; (2) to provide chemopreventive effects in patients with PSC, prior colorectal dysplasia, extensive and long-standing disease, or a family history of colorectal cancer occurring at a young age¹¹⁴⁻¹¹⁶; (3) to accommodate patient preference (no-cebo effect); or (4) for reimbursement (e.g., in Taiwan, reimbursement for biologics is limited to 1 year; consequently, physicians may opt to maintain 5-ASA therapy to facilitate subse-

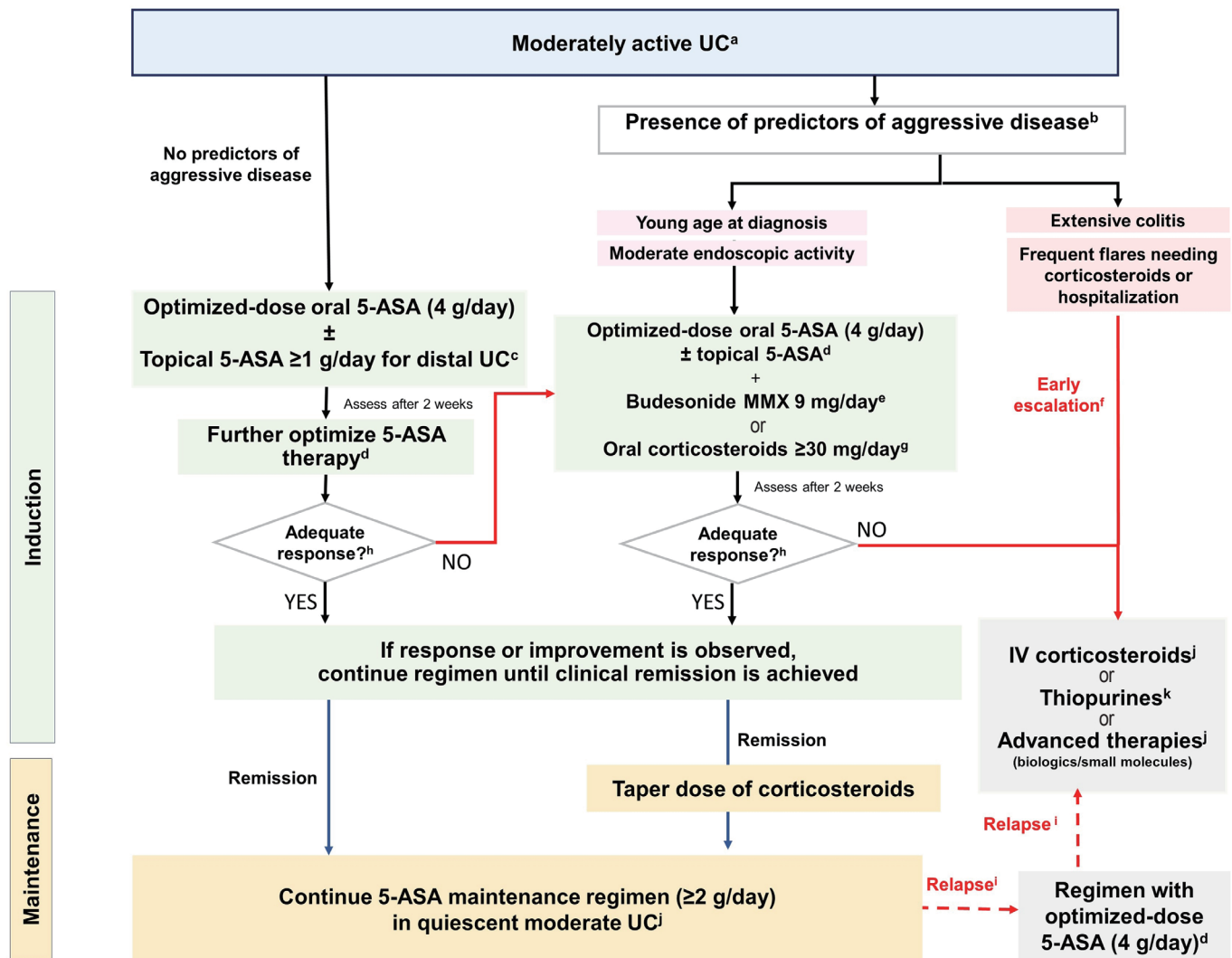


Fig. 1. Proposed treatment algorithm for patients with moderate ulcerative colitis (UC). ^aAccording to modified Truelove and Witts criteria: 4–6 bowel movements/day, temperature $\leq 37.8^{\circ}\text{C}$, pulse ≤ 90 beats/min, hemoglobin ≥ 10.5 g/dL, and C-reactive protein ≤ 30 mg/L. Additional assessments to measure disease activity may take into account clinical presentation, patient-reported symptoms, and objective/laboratory criteria. In the absence of a validated definition for moderate UC, classification of moderate UC is subject to physicians' preferences and judgement; ^bThe weightage for each predictor varies, and management strategies are determined at the physician's discretion; ^cRectal 5-aminosalicylate (5-ASA) at a dose of ≥ 1 g/day at induction is recommended for patients with distal UC, specifically those with proctosigmoiditis or proctitis; ^dIf 5-ASA dose has been maximized to ≥ 4 g/day, and topical 5-ASA therapy has been added and similarly optimized (e.g., ≥ 1 g/day rectal 5-ASA), also optimize patient adherence, extend treatment duration, and switch 5-ASA formulation¹⁷; ^eBudesonide multimatrix (MMX) can be considered before systemic corticosteroids. In some areas, beclomethasone dipropionate is being used instead of budesonide MMX; ^fEarly escalation to immunomodulators such as thiopurine may be required for patients who are intolerant of 5-ASA or with specific strong predictors of aggressive disease; ^gFor patients with predictors of aggressive disease, consider adding 30–40 mg/day oral corticosteroids to 5-ASA. For patients with an inadequate response to 5-ASA therapy, an add-on dose of ≥ 40 mg/day oral corticosteroids could be considered; ^hInadequate response: failure to achieve $\geq 50\%$ decrease in rectal bleeding and stool frequency, per an adaptation of STRIDE-II consensus recommendations⁴⁹; ⁱRelapse: failure to achieve rectal bleeding = 0, stool frequency = 0, or Mayo Endoscopic Subscore < 3 , per an adaptation of STRIDE-II consensus recommendations⁴⁹; ^jFor maintenance therapy in moderate endoscopic activity: after tapering corticosteroids, an immunomodulator such as thiopurine should be considered in addition to 5-ASA; ^kFor corticosteroid-dependent patients: 5-ASA (particularly topical) can be continued for symptom control until onset of action of treatment, for chemoprotective effects, to meet reimbursement criteria, to control disease activity after de-escalation/treatment holiday, or if patient prefers. IV, intravenous; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease. Adapted from Le Berre C, et al. Expert Opin Biol Ther 2020;20:363–378, with permission from Taylor & Francis.⁴⁵

quent de-escalation from advanced therapeutic approaches). It should be noted that discontinuation of 5-ASA therapy has not been shown to elevate risk of adverse events in patients who are initiating anti-TNF therapy.¹¹⁷

5. Moderate UC Treatment Algorithm

A proposed treatment algorithm for moderate UC is presented in Fig. 1, which takes into account current practices and recommendations of the APMA IBD Coalition.

LIMITATIONS OF THE STUDY

We acknowledge the inherent limitations associated with the methodology employed in this study. The selection of experts could be influenced by their specific areas of expertise and the resources at their disposal. Also, there is no formal assessment of expert consensus, such as the utilization of the Delphi method or the establishment of a predetermined threshold to ascertain agreement with each recommendation. Nevertheless, potential recommendations which received vocal disagreement during the meeting were not developed further for inclusion in this article. It is imperative to acknowledge that the deliberations conducted during the meeting and the subsequent suggestions put forth have a firm foundation within current evidence. To foster substantive discussion, a proficient moderator facilitated the sessions, encouraging active participation and open dialogue among all participants with expertise in the subject matter. While acknowledging the potential benefits of utilizing quantitative metrics to assess agreement, we contend that the qualitative methodology employed holds promise in generating valuable expert recommendations for the wider medical community.

SUMMARY OF INSIGHTS AND FUTURE PERSPECTIVES

Moderate UC represents a distinct phenotype that necessitates clinical attention. Existing guidelines lack a consistent definition and comprehensive recommendations for moderate UC treatment, which may contribute to indiscriminate and premature escalation to advanced therapies, which may have adverse consequences for the patient. This article may guide the identification of patients with moderate UC and treatment by way of a simplified treatment algorithm, emphasizing the importance of timely and accurate risk stratification in order to devise appropriate treatment strategies. The Truelove and Witts criteria,

along with other tools and biomarkers for measuring disease activity, can be used to identify patients who have moderate UC, in the absence of universally accepted criteria.

5-ASA remains a first-line treatment for patients with moderate UC. In patients with moderate UC who do not exhibit predictors of aggressive disease, 5-ASA treatment can be optimized through careful selection of an appropriate product formulation (e.g., prolonged-release formulations, granule form), the use of an effective optimized dose (4 g/day), and the implementation of a once-daily regimen, while educational and behavioral interventions may be utilized to enhance patient adherence. 5-ASA treatment should be maintained for as long as the patient responds to the treatment. Patients with inadequate response to the induction regimen despite optimization may benefit from add-on oral corticosteroids or budesonide MMX prior to escalation to immunomodulators or advanced therapies.

It is hoped that addressing the unique challenges and complexities associated with moderate UC management will contribute to the development of tailored therapeutic strategies that align with individual patient needs and preferences, ultimately enhancing the delivery of high-quality care of patients with moderate UC in diverse real-world clinical settings.

ADDITIONAL INFORMATION

Funding Source

This work was supported by an unrestricted educational grant from Ferring Pharmaceuticals.

Conflict of Interest

Akyüz F has received speaker's fees from AbbVie and Janssen. An YK has received speaking and consulting fees from AbbVie, Bristol Myers Squibb, Celltrion, Chiesi, Dr. Falk, Ferring Pharmaceuticals, Janssen, Pfizer, Sandoz, Shire and Takeda; served on advisory boards member for AbbVie, Bristol Myers Squibb, Chiesi, Janssen, NPS Medicine Wise, Microba; received research and educational funding from AbbVie, Celltrion, Dr Falk, Janssen, Pfizer, Sandoz and Takeda. Begun J has served as an advisory board member, consultant, or speaker for AbbVie, Alimentiv, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring Pharmaceuticals, Gilead Sciences, Janssen, Chiesi, Anantara, Pfizer, and Takeda. Has received research funding from AbbVie, Pfizer, and Janssen. Aniwaniwan S has received speaker's fees from Janssen, Ferring Pharmaceuticals, and Takeda, and a fee for attending advisory board/round table

discussions with Sandoz and Takeda. Bui HH has received speaker's fees from Ferring Pharmaceuticals, Janssen and AbbVie. Chan W has received speaker's fees from AbbVie, Ferring Pharmaceuticals and Janssen. Choi CH has served as an advisory board member for AbbVie Korea, Celltrion, Ferring Pharmaceuticals Korea, Samsung Bioepis, Takeda Korea, and Yuhan, and has received research funding from AbbVie Korea, Celltrion, and Takeda Korea. Chopdat N has no conflict of interest to declare. Connor SJ has received honoraria for advisory board participation, speaker's fees, educational support and/or research support from: AbbVie, Amgen, Bristol Myers Squibb, Celltrion, Chiesi, Dr. Falk, Eli Lilly, Ferring Pharmaceuticals, GSK, Janssen, MSD, Organon, Pfizer, Sandoz, Takeda, Agency for Clinical Innovation, Medical Research Future Fund, South-Western Sydney Local Health District, Sydney Partnership for Health, Research and Enterprise (SPHERE) and The Leona M and Harry B Helmsley Charitable Trust. Desai D has served as an advisory board member for Ferring Pharmaceuticals. Flanagan E has received speaker's fees from AbbVie, Ferring Pharmaceuticals, Janssen, Sandoz and Takeda; and received a research grant from Ferring Pharmaceuticals. Kobayashi T has served as an advisory board member, consultant, or speaker for AbbVie, Activaidd, Alfresa Pharma, Alimentiv, Bristol Myers Squibb, Celltrion, Covidien, EA Pharma, Eli Lilly, Ferring Pharmaceuticals, Galapagos, Gilead Sciences, Janssen Pharmaceuticals, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Takeda, and Zeria Pharmaceutical, and has received research funding from AbbVie, Alfresa Pharma, EA Pharma, Gilead Sciences, Kyorin Pharmaceutical, Mochida Pharmaceutical, Nippon Kayaku, Otsuka Holdings, Pfizer, Sekisui Medical, Takeda, and Zeria Pharmaceutical. Lai AYH is an employee of Ferring Pharmaceuticals. Leong RW is an advisory board member of: AbbVie, Aspen, Bristol Myers Squibb, Celgene, Celltrion, Chiesi, Ferring Pharmaceuticals, Glutagen, Hospira, J&J Innovative Medicine, Lilly, Merck Sharpe & Dohme, Novartis, Pfizer, Prometheus Biosciences, Takeda; and is a grant recipient from Celltrion, Shire, Janssen, Takeda, Gastroenterological Society of Australia, Medical Research Future Fund, National Health Medical Research Council, Gutsy Group, Pfizer, Joanna Tiddy Grant University of Sydney and McCusker Charitable Foundation. Leow AHR has received speaker's fees from AstraZeneca, Takeda, Janssen, Ferring Pharmaceuticals, Abbott and Servier, and fees for attending advisory board/round table discussion with AbbVie and Janssen. Leung WK has received speaker's

fees from AbbVie, Ferring Pharmaceuticals and Janssen; and fees for attending advisory boards of AstraZeneca and Biocodex. Limsrivilai J has received speaker's fees from Janssen, Ferring Pharmaceuticals, and Takeda, and fees for attending advisory board/round table discussion with Novartis and Takeda. Muzellina VN has received speaker's fees from Ferring Pharmaceuticals. Ooi CJ has received speaker's fees from Janssen, Ferring, Dr. Falk, Celltrion and AbbVie, and fees for attending advisory board/round table discussion with AbbVie, Pfizer, Janssen and Takeda. Peddi K has served as advisory board member to Janssen, Takeda and Ferring Pharmaceuticals. Zhihua R has no conflict of interest to declare. Wei SC has received speaker's fees from AbbVie, Bristol Myers Squibb, Celltrion, Ferring Pharmaceuticals, Janssen, Pfizer, Takeda and Tanabe, and fees for attending advisory board/round table discussions with AbbVie, Bristol Myers Squibb, Celltrion, Cornerstones, Ferring Pharmaceuticals, Janssen, Pfizer, Sanofi and Takeda. Sollano J has received speaker's fees from Johnson & Johnson, Celltrion, A Menarini, Ferring Pharmaceuticals and Takeda. Teo MMH is an employee of Ferring Pharmaceuticals. Wu K has served as an advisory board member, consultant, or speaker for AbbVie, Bristol Myers Squibb, Ferring Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, JIMRO, Pfizer, Takeda, IPSEN and BioRey and CMS. Ye BD has served as an advisory board member for AbbVie Korea, Bristol Myers Squibb Pharmaceutical Korea Ltd., Celltrion, Ferring Korea, Janssen Korea, Pfizer Korea, Samsung Bioepis, Takeda, Takeda Korea, and Yuhan; a consultant for Chong Kun Dang Pharm, CJ Red BIO, Curacle, Daewoong Pharm, Dong-A ST, Im scout, IQVIA, Korea Otsuka Pharm, Korea United Pharm, Medtronic Korea, NanoEntek, and ORGANOIDSCIENCES Ltd.; a speaker for AbbVie Korea, Bristol Myers Squibb Pharmaceutical Korea Ltd., Celltrion, Cornerstones Health, Curacle, Eisai Korea, Ferring Korea, Samsung Bioepis, Janssen Korea, Pfizer Korea, and has received research funding from Celltrion, Pfizer Korea, and Takeda Korea.

Ooi CJ and Wei SC are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

Not applicable.

Author Contributions

Conceptualization: Lai AYH, Teo MMH. Funding acquisition:

Lai AYH, Teo MMH. Methodology: Lai AYH, Teo MMH. Project administration: Lai AYH, Teo MMH. Visualization: all authors. Writing - original draft: all authors. Writing - review & editing: all authors. Approval of final manuscript: all authors. Authors are arranged in alphabetical order of their last names, except for the corresponding author who is listed last.

Additional Contributions

Medical writing support was provided by Svetha Sankar, BSc, BVMS, and Khi Khi Choo, BSc, PhD, ISMPP CMPP, of MIMS Pte Ltd (Singapore) and was funded by Ferring Pte Ltd.

ORCID

Akyüz F	https://orcid.org/0000-0001-7498-141X
An YK	https://orcid.org/0000-0002-1458-8015
Begun J	https://orcid.org/0000-0001-5256-7672
Aniwan S	https://orcid.org/0000-0002-2730-2450
Bui HH	https://orcid.org/0000-0003-2436-6712
Chan W	https://orcid.org/0000-0002-8884-3381
Choi CH	https://orcid.org/0000-0001-7089-532X
Chopdat N	https://orcid.org/0000-0001-8548-497X
Connor SJ	https://orcid.org/0000-0001-5606-0270
Desai D	https://orcid.org/0000-0002-9741-5549
Flanagan E	https://orcid.org/0000-0002-3911-4780
Kobayashi T	https://orcid.org/0000-0002-2073-4234
Lai AYH	https://orcid.org/0009-0004-1092-6517
Leong RW	https://orcid.org/0000-0001-5944-3488
Leow AHR	https://orcid.org/0000-0003-1752-0435
Leung WK	https://orcid.org/0000-0002-5993-1059
Limsrivilai J	https://orcid.org/0000-0001-5867-0312
Muzellina VN	https://orcid.org/0000-0003-4949-7145
Ooi CJ	https://orcid.org/0000-0001-8961-5455
Peddi K	https://orcid.org/0000-0002-4524-9366
Ran Z	https://orcid.org/0000-0001-6388-6206
Wei SC	https://orcid.org/0000-0002-5017-5840
Sollano J	https://orcid.org/0000-0003-3227-1983
Wu K	https://orcid.org/0000-0002-0699-9666
Ye BD	https://orcid.org/0000-0001-6647-6325

REFERENCES

1. Ko CW, Singh S, Feuerstein JD, et al. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. *Gastroenterology* 2019;156:748-764.
2. Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Coli-*

3. Wang Q, Chen MR, Hao JW, et al. AB1675 Deep phenotyping of immune microenvironment in ulcerative colitis by integrative systems analysis. *Ann Rheum Dis* 2023;82:2074-2075.
4. Mortlock S, Lord A, Montgomery G, et al. An extremes of phenotype approach confirms significant genetic heterogeneity in patients with ulcerative colitis. *J Crohns Colitis* 2023;17:277-288.
5. Yang H, Rotter JJ, Toyoda H, et al. Ulcerative colitis: a genetically heterogeneous disorder defined by genetic (HLA class II) and subclinical (antineutrophil cytoplasmic antibodies) markers. *J Clin Invest* 1993;92:1080-1084.
6. Ran Z, Wu K, Matsuoka K, et al. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology practice recommendations for medical management and monitoring of inflammatory bowel disease in Asia. *J Gastroenterol Hepatol* 2021;36:637-645.
7. Na SY, Choi CH, Song EM, et al. Korean clinical practice guidelines on biologics and small molecules for moderate-to-severe ulcerative colitis. *Intest Res* 2023;21:61-87.
8. Jakobsen C, Bartek J, Wewer V, et al. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease: a population-based study. *Aliment Pharmacol Ther* 2011;34:1217-1224.
9. Jess T, Riis L, Vind I, et al. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm Bowel Dis* 2007;13:481-489.
10. Wang Y, Parker CE, Bhanji T, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016;4:CD000543.
11. Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J* 1955;2:1041-1048.
12. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462-2476.
13. UEG week 2019 poster presentations. *United European Gastroenterol J* 2019;7(8_suppl):189-1030.
14. Chu X, Biao Y, Liu C, et al. Network meta-analysis on efficacy and safety of different biologics for ulcerative colitis. *BMC Gastroenterol* 2023;23:346.
15. Paridaens K, Fullarton JR, Travis SP. Efficacy of oral prolonged-release mesalazine in moderately active ulcerative colitis. *JGH Open* 2023;7:516-519.
16. Burisch J, Safroneeva E, Laoun R, Ma C. Lack of benefit for early escalation to advanced therapies in ulcerative colitis: *tis* 2022;16:2-17.

- critical appraisal of current evidence. *J Crohns Colitis* 2023; 17:2002-2011.
17. Taylor KM, Irving PM. Optimization of conventional therapy in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2011; 8:646-656.
18. Louis E, Paridaens K, Al Awadhi S, et al. Modelling the benefits of an optimised treatment strategy for 5-ASA in mild-to-moderate ulcerative colitis. *BMJ Open Gastroenterol* 2022;9: e000853.
19. Chebli JM, Gaburri PD, Chebli LA, et al. A guide to prepare patients with inflammatory bowel diseases for anti-TNF- α therapy. *Med Sci Monit* 2014;20:487-498.
20. Mak JW, Sung JJ. The use of biologics and biosimilar in Asian patients with IBD: are we ready? *J Gastroenterol Hepatol* 2019; 34:1269-1270.
21. Mak JW, Ho AH, Ng SC. IBD barriers across the continents: East Asia. *Therap Adv Gastroenterol* 2023;16:17562848231212089.
22. Farraj KL, Pellegrini JR, Munshi RF, et al. Chronic steroid use: an overlooked impact on patients with inflammatory bowel disease. *JGH Open* 2022;6:910-914.
23. Indo-Pacific Centre for Health Security. State of the region 2019: health security in the Indo-Pacific [Internet]. c2022 [cited 2024 Jun 1]. <https://indopacifichealthsecurity.dfat.gov.au/sites/default/files/2022-07/Indo-Pacific%20Health%20Security%20-%20State%20of%20the%20Region%202019.pdf>
24. Chakaya J, Petersen E, Nantanda R, et al. The WHO global tuberculosis 2021 report: not so good news and turning the tide back to End TB. *Int J Infect Dis* 2022;124 Suppl 1:S26-S29.
25. GBD 2019 Hepatitis B Collaborators. Global, regional, and national burden of hepatitis B, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Gastroenterol Hepatol* 2022;7:796-829.
26. Panés J, Lindsay JO, Teich N, et al. Five-year safety data from OPUS, a European observational safety registry for adults with ulcerative colitis treated with originator infliximab [Remicade®] or conventional therapy. *J Crohns Colitis* 2019;13: 1148-1157.
27. Wei SC. Differences in the public medical insurance systems for inflammatory bowel disease treatment in Asian countries. *Intest Res* 2016;14:218-223.
28. Low D, Swarup N, Okada T, Mizoguchi E. Landscape of inflammatory bowel disease in Singapore. *Intest Res* 2022;20:291-296.
29. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology* 2017;153: 827-834.
30. Scott FI, Lichtenstein GR. Therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease. *Curr Treat Options Gastroenterol* 2014;12:59-75.
31. Marsal J, Barreiro-de Acosta M, Blumenstein I, Cappello M, Bazin T, Sebastian S. Management of non-response and loss of response to anti-tumor necrosis factor therapy in inflammatory bowel disease. *Front Med (Lausanne)* 2022;9:897936.
32. Savelkoul EH, Thomas PW, Derikx LA, den Broeder N, Rönkens TE, Hoentjen F. Systematic review and meta-analysis: loss of response and need for dose escalation of infliximab and adalimumab in ulcerative colitis. *Inflamm Bowel Dis* 2023;29:1633-1647.
33. Schmidt E, Kochhar G, Hartke J, et al. Predictors and management of loss of response to vedolizumab in inflammatory bowel disease. *Inflamm Bowel Dis* 2018;24:2461-2467.
34. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A Simple clinical colitis activity index. *Gut* 1998;43:29-32.
35. Walsh AJ, Ghosh A, Brain AO, et al. Comparing disease activity indices in ulcerative colitis. *J Crohns Colitis* 2014;8:318-325.
36. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: a randomized study. *N Engl J Med* 1987;317:1625-1629.
37. Caron B, Jairath V, D'Amico F, et al. Definition of mild to moderate ulcerative colitis in clinical trials: a systematic literature review. *United European Gastroenterol J* 2022;10:854-867.
38. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005;100:2478-2485.
39. Sandborn WJ, Regula J, Feagan BG, et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. *Gastroenterology* 2009;137:1934-1943.
40. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012;61:535-542.
41. Xie T, Zhang T, Ding C, et al. Ulcerative Colitis Endoscopic Index of Severity (UCEIS) versus Mayo Endoscopic Score (MES) in guiding the need for colectomy in patients with

- acute severe colitis. *Gastroenterol Rep (Oxf)* 2018;6:38-44.
42. Pabla BS, Schwartz DA. Assessing severity of disease in patients with ulcerative colitis. *Gastroenterol Clin North Am* 2020;49:671-688.
 43. Kedia S, Ahuja V, Tandon R. Management of acute severe ulcerative colitis. *World J Gastrointest Pathophysiol* 2014;5:579-588.
 44. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017;11:769-784.
 45. Le Berre C, Roda G, Nedeljkovic Protic M, Danese S, Peyrin-Biroulet L. Modern use of 5-aminosalicylic acid compounds for ulcerative colitis. *Expert Opin Biol Ther* 2020;20:363-378.
 46. Kishi M, Hirai F, Takatsu N, et al. A review on the current status and definitions of activity indices in inflammatory bowel disease: how to use indices for precise evaluation. *J Gastroenterol* 2022;57:246-266.
 47. Ooi CJ, Hilmi I, Banerjee R, et al. Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. *Intest Res* 2019;17:285-310.
 48. Heckman BW, Mathew AR, Carpenter MJ. Treatment burden and treatment fatigue as barriers to health. *Curr Opin Psychol* 2015;5:31-36.
 49. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the study of IBD (IOIBD). Determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021; 160:1570-1583.
 50. Viscido A, Valvano M, Stefanelli G, et al. Systematic review and meta-analysis: the advantage of endoscopic Mayo score 0 over 1 in patients with ulcerative colitis. *BMC Gastroenterol* 2022;22:92.
 51. Min Ho PY, Hu W, Lee YY, et al. Health-related quality of life of patients with inflammatory bowel disease in Singapore. *Intest Res* 2019;17:107-118.
 52. Yarlaz A, Willian MK, Nag A. The impact of clinical symptoms and endoscopic and histologic disease activity on health-related quality of life in patients with ulcerative colitis following treatment with multimatrix mesalazine. *Qual Life Res* 2021; 30:1925-1938.
 53. Reinink AR, Lee TC, Higgins PD. Endoscopic mucosal healing predicts favorable clinical outcomes in inflammatory bowel disease: a meta-analysis. *Inflamm Bowel Dis* 2016;22: 1859-1869.
 54. Christensen B, Hanauer SB, Erlich J, et al. Histologic normalization occurs in ulcerative colitis and is associated with improved clinical outcomes. *Clin Gastroenterol Hepatol* 2017; 15:1557-1564.
 55. Bryant RV, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut* 2016;65:408-414.
 56. Patel KV, Salmon P, Marin-Jiménez I, et al. P416 The impact of remission on healthcare resource utilisation and costs amongst patients with inflammatory bowel disease in France, Germany, Italy, Spain, and the United Kingdom. *J Crohn Colitis* 2023;17(Suppl 1):i544-i546.
 57. Vaizey CJ, Gibson PR, Black CM, et al. Disease status, patient quality of life and healthcare resource use for ulcerative colitis in the UK: an observational study. *Frontline Gastroenterol* 2014;5:183-189.
 58. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;68:s1-s106.
 59. Ouyang Q, Tandon R, Goh KL, et al. Management consensus of inflammatory bowel disease for the Asia-Pacific region. *J Gastroenterol Hepatol* 2006;21:1772-1782.
 60. Ling KL, Hilmi I, Raja Ali RA, et al. Asian Pacific Association of Gastroenterology (APAGE) Inflammatory Bowel Disease (IBD) Working Party guidelines on IBD management during the COVID-19 pandemic. *JGH Open* 2020;4:320-323.
 61. 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;16:343-356.
 62. Ng SC, Zeng Z, Niewiadomski O, et al. Early course of inflammatory bowel disease in a population-based inception cohort study from 8 countries in Asia and Australia. *Gastroenterology* 2016;150:86-95.
 63. Vegh Z, Burisch J, Pedersen N, et al. Incidence and initial disease course of inflammatory bowel diseases in 2011 in Europe and Australia: results of the 2011 ECCO-EpiCom inception cohort. *J Crohns Colitis* 2014;8:1506-1515.
 64. Barberio B, Segal JP, Quraishi MN, Black CJ, Savarino EV, Ford AC. Efficacy of oral, topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and network meta-analysis. *J Crohns Colitis* 2021;15:1184-1196.
 65. Battat R, Duijvestein M, Guizzetti L, et al. Histologic healing rates of medical therapies for ulcerative colitis: a systematic

- review and meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2019;114:733-745.
66. Römkens TE, Kampschreur MT, Drenth JP, van Oijen MG, de Jong DJ. High mucosal healing rates in 5-ASA-treated ulcerative colitis patients: results of a meta-analysis of clinical trials. *Inflamm Bowel Dis* 2012;18:2190-2198.
67. Ardizzone S, Cassinotti A, Duca P, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol* 2011;9:483-489.
68. Bokemeyer B, Hommes D, Gill I, Broberg P, Dignass A. Mesalazine in left-sided ulcerative colitis: efficacy analyses from the PODIUM trial on maintenance of remission and mucosal healing. *J Crohns Colitis* 2012;6:476-482.
69. Lichtenstein GR, Barrett AC, Bortey E, Paterson C, Forbes WP. Long-term safety and tolerability of once-daily mesalamine granules in the maintenance of remission of ulcerative colitis. *Inflamm Bowel Dis* 2014;20:1399-1406.
70. Sehgal P, Colombel JF, Aboubakr A, Narula N. Systematic review: safety of mesalazine in ulcerative colitis. *Aliment Pharmacol Ther* 2018;47:1597-1609.
71. Burri E, Maillard MH, Schoepfer AM, et al. Treatment algorithm for mild and moderate-to-severe ulcerative colitis: an update. *Digestion* 2020;101 Suppl 1:2-15.
72. Katz S, Pasquale M. Daily dosing of delayed release mesalamine prior to immunosuppressive use. *Am J Gastroenterol* 2009;104:S444.
73. Hiwatashi N, Suzuki Y, Mitsuyama K, Munakata A, Hibi T. Clinical trial: effects of an oral preparation of mesalazine at 4 g/day on moderately active ulcerative colitis. A phase III parallel-dosing study. *J Gastroenterol* 2011;46:46-56.
74. West R, Russel M, Bodelier A, et al. Lower risk of recurrence with a higher induction dose of mesalazine and longer duration of treatment in ulcerative colitis: results from the Dutch, non-interventional, IMPACT study. *J Gastrointest Liver Dis* 2022;31:18-24.
75. Paupard T, Gonzalez F, Caron B, Siproudhis L, Peyrin-Biroulet L. Real-world evidence of quality of life improvement in patients with distal ulcerative colitis treated by mesalazine: the Quartz study. *Eur J Gastroenterol Hepatol* 2022;34:1203-1209.
76. Flourié B, Hagège H, Tucet G, et al. Randomised clinical trial: once- vs. twice-daily prolonged-release mesalazine for active ulcerative colitis. *Aliment Pharmacol Ther* 2013;37:767-775.
77. Frieri G, Giacomelli R, Pimpo M, et al. Mucosal 5-aminosalicylic acid concentration inversely correlates with severity of colonic inflammation in patients with ulcerative colitis. *Gut* 2000;47:410-414.
78. De Vos M. Clinical pharmacokinetics of slow release mesalazine. *Clin Pharmacokinet* 2000;39:85-97.
79. Seibold F, Fournier N, Beglinger C, et al. Topical therapy is underused in patients with ulcerative colitis. *J Crohns Colitis* 2014;8:56-63.
80. Nguyen NH, Fumery M, Dulai PS, et al. Comparative efficacy and tolerability of pharmacological agents for management of mild to moderate ulcerative colitis: a systematic review and network meta-analyses. *Lancet Gastroenterol Hepatol* 2018;3:742-753.
81. Marteau P, Probert CS, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut* 2005;54:960-965.
82. Cohen RD, Woseth DM, Thisted RA, Hanauer SB. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000;95:1263-1276.
83. Takeshima F, Matsumura M, Makiyama K, et al. Efficacy of long-term 4.0 g/day mesalazine (Pentasa) for maintenance therapy in ulcerative colitis. *Med Sci Monit* 2014;20:1314-1318.
84. Chapman TP, Frias Gomes C, Louis E, Colombel JF, Satsangi J. Review article: withdrawal of 5-aminosalicylates in inflammatory bowel disease. *Aliment Pharmacol Ther* 2020;52:73-84.
85. Sood A, Ahuja V, Midha V, et al. Colitis and Crohn's Foundation (India) consensus statements on use of 5-aminosalicylic acid in inflammatory bowel disease. *Intest Res* 2020;18:355-378.
86. Can G, Yozgat A, Tezel A, Ünsal G, Soylu AR. Beliefs about medicines and adherence to treatment in Turkish patients with inflammatory bowel disease. *Turk J Gastroenterol* 2022; 33:743-750.
87. Bhatt J, Patil S, Joshi A, Abraham P, Desai D. Self-reported treatment adherence in inflammatory bowel disease in Indian patients. *Indian J Gastroenterol* 2009;28:143-146.
88. Kawakami A, Tanaka M, Nishigaki M, et al. Relationship between non-adherence to aminosalicylate medication and the risk of clinical relapse among Japanese patients with ulcerative colitis in clinical remission: a prospective cohort study. *J Gastroenterol* 2013;48:1006-1015.
89. Kim SB, Kim KO, Jang BI, et al. Patients' beliefs and attitudes

- about their treatment for inflammatory bowel disease in Korea. *J Gastroenterol Hepatol* 2016;31:575-580.
90. Kane SV. Overcoming adherence issues in ulcerative colitis. *Gastroenterol Hepatol (N Y)* 2007;3:795-799.
 91. Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2006;23:577-585.
 92. Lee J, Jee SR, Kim HW, et al. Factors associated with low adherence to oral 5-aminosalicylic acid in patients with ulcerative colitis. *PLoS One* 2019;14:e0214129.
 93. Nishikawa AM, Paladini L, Delfini R, Kotze PG, Clark O. Decision tree construction and cost-effectiveness analysis of treatment of ulcerative colitis with Pentasa® mesalazine 2 g sachet. *Arq Gastroenterol* 2013;50:297-303.
 94. Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med* 2003;114:39-43.
 95. Perry J, Chen A, Kariyawasam V, et al. Medication non-adherence in inflammatory bowel diseases is associated with disability. *Intest Res* 2018;16:571-578.
 96. Srivastava K, Arora A, Kataria A, Cappelleri JC, Sadosky A, Peterson AM. Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis. *Patient Prefer Adherence* 2013;7:419-434.
 97. Dignass AU, Bokemeyer B, Adamek H, et al. Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;7:762-769.
 98. Connolly MP, Nielsen SK, Currie CJ, Poole CD, Travis SP. An economic evaluation comparing once daily with twice daily mesalazine for maintaining remission based on results from a randomised controlled clinical trial. *J Crohns Colitis* 2009;3:32-37.
 99. Laube R, Selinger C, Leong RW. Medication adherence in women with IBD of childbearing age likely associated with disease knowledge. *Therap Adv Gastroenterol* 2022;15:17562848221144088.
 100. de Jong MJ, Boonen A, van der Meulen-de Jong AE, et al. Cost-effectiveness of telemedicine-directed specialized vs standard care for patients with inflammatory bowel diseases in a randomized trial. *Clin Gastroenterol Hepatol* 2020;18:1744-1752.
 101. Elkjaer M, Shuhaibar M, Burisch J, et al. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. *Gut* 2010;59:1652-1661.
 102. Severs M, Zuithoff PN, Mangen MJ, et al. Assessing self-reported medication adherence in inflammatory bowel disease: a comparison of tools. *Inflamm Bowel Dis* 2016;22:2158-2164.
 103. Tiao DK, Chan W, Jeganathan J, et al. Inflammatory bowel disease pharmacist adherence counseling improves medication adherence in Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2017;23:1257-1261.
 104. Nakagawa S, Okaniwa N, Mizuno M, et al. Treatment adherence in patients with ulcerative colitis is dependent on the formulation of 5-aminosalicylic acid. *Digestion* 2019;99:133-139.
 105. Yagisawa K, Kobayashi T, Ozaki R, et al. Randomized, cross-over questionnaire survey of acceptabilities of controlled-release mesalazine tablets and granules in ulcerative colitis patients. *Intest Res* 2019;17:87-93.
 106. Hiraoka S, Fujiwara A, Toyokawa T, et al. Multicenter survey on mesalamine intolerance in patients with ulcerative colitis. *J Gastroenterol Hepatol* 2021;36:137-143.
 107. Suzuki K, Kakuta Y, Naito T, et al. Genetic background of mesalamine-induced fever and diarrhea in Japanese patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2022;28:21-31.
 108. Campieri M, Ferguson A, Doe W, Persson T, Nilsson LG. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997;41:209-214.
 109. Bonovas S, Nikolopoulos GK, Lytras T, Fiorino G, Peyrin-Biroulet L, Danese S. Comparative safety of systemic and low-bioavailability steroids in inflammatory bowel disease: systematic review and network meta-analysis. *Br J Clin Pharmacol* 2018;84:239-251.
 110. Danese S, Bonovas S, Peyrin-Biroulet L. Budesonide MMX add-on to 5-aminosalicylic acid therapy in mild-to-moderate ulcerative colitis: a favourable risk-benefit profile. *J Crohns Colitis* 2017;11:767-768.
 111. Rubin DT, Cohen RD, Sandborn WJ, et al. Budesonide multi-matrix is efficacious for mesalamine-refractory, mild to moderate ulcerative colitis: a randomised, placebo-controlled trial. *J Crohns Colitis* 2017;11:785-791.
 112. Lichtenstein GR, Travis S, Danese S, et al. Budesonide MMX for the induction of remission of mild to moderate ulcerative colitis: a pooled safety analysis. *J Crohns Colitis* 2015;9:738-746.
 113. Ryrfeldt A, Andersson P, Edsbäcker S, Tönnesson M, Davies D, Pauwels R. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur J Respir Dis Suppl* 1982;122:86-

- 95.
114. Qiu X, Ma J, Wang K, Zhang H. Chemopreventive effects of 5-aminosalicylic acid on inflammatory bowel disease-associated colorectal cancer and dysplasia: a systematic review with meta-analysis. *Oncotarget* 2017;8:1031-1045.
115. Hsiao SW, Yen HH, Chen YY. Chemoprevention of colitis-associated dysplasia or cancer in inflammatory bowel disease. *Gut Liver* 2022;16:840-848.
116. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and meta-analysis of observational studies. *Am J Gastroenterol* 2005;100:1345-1353.
117. Ungaro RC, Limketkai BN, Jensen CB, et al. Stopping 5-aminosalicylates in patients with ulcerative colitis starting biologic therapy does not increase the risk of adverse clinical outcomes: analysis of two nationwide population-based cohorts. *Gut* 2019;68:977-984.