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Definition of mild to moderate ulcerative colitis in clinical trials: A systematic literature review

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Abstract

We performed a systematic review to investigate the definition of mild to moderate active ulcerative colitis (UC), and to describe predictors of good response to treatment in clinical trials assessing 5-ASA and/or budesonide. Thirty-nine randomized controlled trials were included. The UC Disease Activity Index (UCDAI) was the most frequent score used for defining mild to moderate active UC (16 studies, 41%), followed by Clinical Activity Index in 11 studies (28.2%). Four different cut-offs were used to define mild to moderate active UC using the UCDAI. The most frequently reported predictors of good response to treatment was a mild and moderate disease activity. There is heterogeneity in the definition of mild to moderate active UC in randomized clinical trials. A standardized definition of mild to moderate active UC used for inclusion of patients in clinical trials is needed.

KEYWORDS

definition, mild, moderate, predictive factor, ulcerative colitis

INTRODUCTION

The development of novel therapeutics and a better understanding of biological pathways of disease had resulted in improved management of patients with ulcerative colitis (UC).[1] In the last decades, the treatment targets have also evolved from symptom control to clinical remission and then to endoscopic remission aiming at achieving more ambitious goals and an ever-deeper remission.[2,3] Although the evaluation of symptom based disease activity is subjective and less reliable than more objective data such as endoscopy, normalization of symptoms is the most desired target by patients as it impacts their quality of life.[4] The severity of UC has historically been dichotomized into arbitrary categories, specifically mild-to-moderate and moderate-to-severe, depending on number of daily stools, amount of rectal bleeding, vital signs, physician's assessment, and endoscopic evaluation.[5] Several scores have been developed to quantify and standardize the evaluation of clinical disease activity including the Simple Colitis Clinical Activity Index, the Mayo Clinic Score (MCS) (and its modifications), and the Truelove and Witts' criteria for severe disease.[4,6–10] These classifications allow stratification of disease activity, guide the selection of the optimal therapeutic option for each patient setting and help to monitor the response to treatment.[11] There is no consensus about the definition of mild to moderate disease activity in UC (Table 1).[1,12,13] The mainstay of therapy for mild to moderate UC is the 5-aminosalicylic acid (5-ASA) class of medications.[12] The first line therapy for UC patients with exclusively rectal disease is topical 5-ASA while oral 5-ASA alone or in combination with topical therapy is preferred in subjects with left-side or extensive UC.[1] Patients with inadequate response to optimized 5-ASA require therapy escalation to budesonide multimatrix system (MMX) or oral prednisone.[12] The lack of a commonly accepted definition of mild to moderate UC makes clinical trial data heterogeneous and non-replicable, and influences clinical practice by exposing patients to under or over-treatment.[14]

For this reason, we conducted a systematic literature review to investigate the definition of mild to moderate active UC and to describe predictive factors of response to treatment in randomized controlled clinical trials assessing 5-ASA and/or budesonide.

METHODS

We conducted a systematic review in accordance with the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting of systematic reviews incorporating network meta-analysis.[15,16]

Search strategy

We searched for randomized controlled trials using Pubmed/Embase, and Scopus databases from January 2000 to January 2022. The following Medical Subject Heading terms alone or matched with the Boolean operators "AND" or "OR" were used: "IBD", "inflammatory bowel disease", "UC", "ulcerative colitis", "5-ASA", "5-aminosalicylic acid", "mesalazine", "mesalamine", "budesonide", "budesonide MMX", "budesonide multimatrix", "mild", "moderate". We focused on 5-ASA and budesonide because these are the only agents established in practice in mild to moderate UC.

Two authors (BC and FD) independently scrutinized titles and abstracts to identify eligible studies. Subsequently, full-text articles were examined for inclusion. In addition, a hand-search of the bibliographic lists of selected manuscripts was performed to identify the studies missing from the electronic search. Any disagreements were resolved through discussion between all co-authors.

Selection criteria

The inclusion criteria were: (a) studies conducted in patients with mild to moderate active UC; (b) randomized controlled trial; (c) study assessing 5-ASA and/or budesonide; (d) study published in English. Only full text articles were included. All editorials, notes, comments, letters, or review articles were ineligible.

Data extraction

After screening for eligible studies, we extracted data regarding study and patient characteristics, study design, drug exposure, definition of mild to moderate active UC, primary endpoint for evaluation

TABLE 1 Current definitions on mild to moderate active ulcerative colitis (UC) in guidelines

IBD organization	Year	Definition of mild to moderate ulcerative colitis
American gastroenterological association	2019	Fewer than 4–6 bowel movements per day, mild-moderate rectal bleeding, absence of constitutional symptoms, low overall inflammatory burden, and absence of features suggestive of high inflammatory activity based upon truelove and Witt's criteria and the Mayo clinic score
British society of gastroenterology	2019	Mayo score between 3 and 10
European Crohn's and colitis organisation	2017	Not applicable

Abbreviation: IBD, Inflammatory Bowel Disease.

of treatment efficacy, and predictive factors of response to treatment when reported.

Quality of studies

The Jadad score was used to measure the quality of randomized clinical trials. High quality studies were defined as Jadad score of three or greater.[17] Two authors (BC and FD) independently graded the studies, and any disagreements were discussed with another author until resolution.

RESULTS

Study characteristics

A summary of the search and selection process is detailed in Figure 1. A total of 3038 citations (Pubmed/Embase: 930; Scopus: 2108) were identified through the search strategy. After removal of duplicates and careful screening of titles and abstracts, 2950 articles were excluded. Additional 49 studies were excluded after full-text review of the manuscripts as they did not meet the inclusion criteria, viz. disease in remission (n = 21), not reporting disease activity (n = 7), observational cohort studies (n = 5), systematic reviews or meta-analysis (n = 5), not evaluating drug efficacy (n = 4), other drug than 5-ASA or budesonide (n = 4), not reporting definition of mild to moderate active UC or predictive factor of response (n = 2), and other language than English (n = 1). Finally, 39 randomized controlled trials were included.[18–56] Table 1 summarizes the main characteristics of the included studies. The study period ranged from 2000 to 2019. A total of 12,046 patients were enrolled. Most studies investigated the efficacy of 5-ASA (33 studies, 84.6%),[18–38,40–48,53,55,56] while budesonide was assessed in

a quarter of cases (10 studies, 25.6%).[39,40,42,45,49–52,54,56] Thirty-five out of 39 studies (89.7%) had a Jadad score of 3 or greater (Table S1).

Definition of mild to moderate active ulcerative colitis

Thirty-nine randomized controlled trials reported the definition of mild to moderate active UC (Table 2). In the majority of studies (33 studies, 84.6%), disease activity was assessed by combined clinical and endoscopic scores[18,19,21,22,24–29,31,32,34,35,37,38,40–56] (Table 3). In 6 studies (15.4%), mild to moderate UC was defined as clinical activity alone.[20,23,30,33,36,39]

The UC Disease Activity Index (DAI) (UCDAI) was the most frequently used score (16 studies, 41%).[19,25,26,31,32,34,41,43,45–50,54,56] Four different UCDAI cut-offs were used to define mild to moderate active UC. More than half of included studies reported an UCDAI ≥4 and ≤10 with a sigmoidoscopy score of ≥1 and a Physician's Global Assessment (PGA) score ≤2 (9 studies,[26,31,32,34,45,49,51,54,56] 56,3%), followed by an UCDAI ≥3 and ≤8 (5 studies,[19,25,41,46,48] 31,3%), between 6 and 8 (1 study,[43] 6,2%) and between 4 and 8 (1 study,[47] 6,2%).

The CAI was used in 11 studies (28.2%).[18,20,21,24,29,33,35,39,40,42,55] Five different CAI cut-offs were used to define mild to moderate active UC. More than half of included studies reported a CAI >4 (6 studies,[18,21,29,33,35,40] 54.5%), followed by a CAI between 6 and 12 (2 studies,[24,55] 18.2%), a CAI ≥6 (1 study,[42] 9.1%), a CAI <14 (1 study,[39] 9.1%), and between 4 and 12 (1 study.[20] 9.1%). Clinical Activity Index was associated with the Endoscopic Index (EI) in 8 studies[18,21,24,29,35,40,42,55]: EI ≥ 4 (7 studies, 87.5%) and >2 (1 study, 12.5%).

The DAI was used in 5 studies (12.8%).[22,27,28,38,44] Five different DAI cut-offs were used to define mild to moderate active UC. One study reported a DAI between 4 and 11 [44] (20%), followed by a DAI
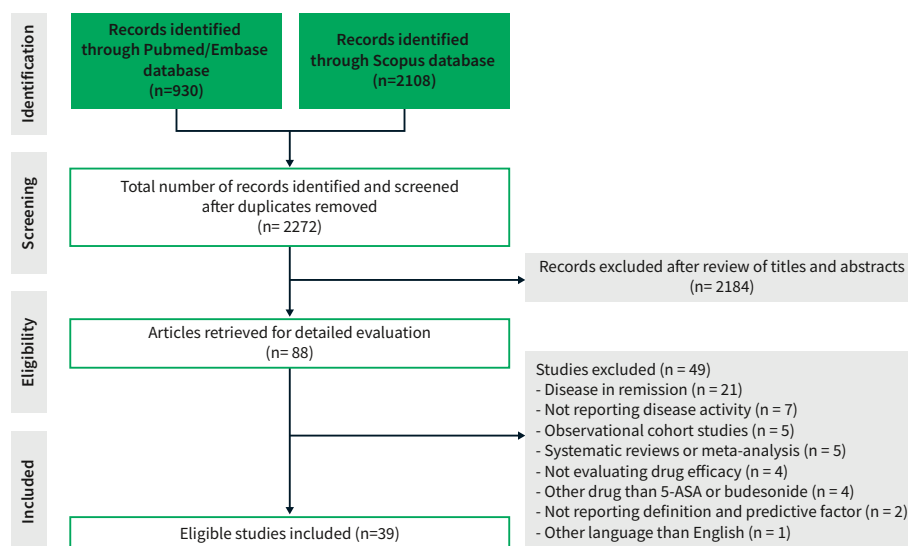

FIGURE 1 Summary of the literature search and selection process (flow diagram)

TABLE 2 Definition of mild to moderate active ulcerative colitis (UC) in randomized clinical trials

First author	Year	Number of patients	Study arms	Definition of mild to moderate ulcerative colitis (inclusion criterion)	Primary endpoint
Pokrotnieks et al.[18]	2000	111	Mesalazine foam enema or placebo enema	CAI >4 and EI of ≥4	Clinical remission at week 6 defined as a CAI ≤4, associated with a decrease of least 2 points from baseline
Farup et al.[19]	2001	227	Mesalazine 4 g daily given as prolonged-release granules in packets of 1 g or prolonged-release tablets of 0.5 g	UCDAI between 3–5 and 6–8	Change from baseline in UCDAI
Vecchi et al.[20]	2001	67	Mesalazine 4 g orally plus placebo enema, or mesalazine 2 g orally plus mesalazine 2 g enema	CAI from 4 to 12	Clinical remission (CAI <4) or clinical remission/improvement (reduction of CAI of 50% from baseline) at week 6 and time to clinical remission/improvement
Raedler et al.[21]	2004	362	Mesalazine micropellets or tablets	CAI for components 1–4 ≥4 and EI ≥4	Clinical remission at week 8 defined as the sum of CAI components 1–4 < or = 2
Gionchetti et al.[22]	2005	217	Beclomethasone dipropionate 3 mg enema o.d. or mesalamine enema daily	DAI ≥3 and ≤10	Decrease in DAI at week 6
Hanauer et al.[23]	2005	386	Mesalamine 2.4 g/day or 4.8 g/day	PGA of 1 or 2	Overall improvement at week 6 defined as either complete remission or a clinical response. Complete remission was defined as normal stool frequency, no rectal bleeding, a PFA score of 0, normal endoscopy findings and a PGA score of 0. Clinical response was defined as a decrease in the PGA score of at least one point from baseline, plus improvement in at least one other clinical assessment parameter (stool frequency, rectal bleeding, PFA or endoscopy findings) and no worsening in any of the other clinical assessments.
Marakhouski et al.[24]	2005	233	1.5 g mesalazine pellets or tablets	CAI of 6–12 and EI ≥4	Complete response (clinical remission) defined as CAI ≤4 at week 8
Marteau et al.[25]	2005	127	Mesalazine enema or placebo	UCDAI score ⩾3 and ⩽8	Remission at week 4 defined as UCDAI <2
D'Haens et al.[26]	2006	38	MMX mesalazine 1.2 or 2.4 or 4.8 g/day	UCDAI score of 4–10 with a sigmoidoscopy score of ≥1 and a PGA score of ≤2	Remission defined as UCDAI < or = 1, a score of 0 for rectal bleeding and stool frequency, and > or = 1 -point reduction in sigmoidoscopy score at week 8
Miner et al.[27]	2006	159	Enema of 120 mg alicaforsen or 240 mg alicaforsen or 4 g mesalazine	DAI of 4–10	Decrease in DAI at week 6 relative to baseline
Biancone et al.[28]	2007	92	Beclomethasone diproprionate enema or foam or mesalazine enema or foam	DAI ranging from 3 to 9, and an endoscopic score ranging from 1 to 2	Remission at week 4, defined as DAI <3

(Continues)

TABLE 2 (Continued)

First author	Year	Number of patients	Study arms	Definition of mild to moderate ulcerative colitis (inclusion criterion)	Primary endpoint
Eliakim et al.[29]	2007	330	Low-volume or high-volume 5-aminosalicylic acid foam	CAI >4 and EI ≥4	Clinical remission defined as CAI < or = 4) at week 6
Hanauer et al.[30]	2007	301	Oral mesalamine 2.4 g/day or 4.8 g/day	PGA score of 1 or 2	Overall improvement at week 6 defined as either complete remission or a clinical response. Complete remission was defined as normal stool frequency, no rectal bleeding, a PFA score of 0, normal endoscopy findings and a PGA score of 0. Clinical response was defined as a decrease in the PGA score of at least one point from baseline, plus improvement in at least one other clinical assessment parameter (stool frequency, rectal bleeding, PFA or endoscopy findings) and no worsening in any of the other clinical assessments.
Kamm et al.[31]	2007	343	MMX mesalamine 2.4 g/day or 4.8 g/day, or ASACOL 2.4 g/day or placebo	Modified UCDAI score of 4–10 with a sigmoidoscopy score ≥1 and a PGA score ≤2	Clinical and endoscopic remission (modified UCDAI of < or = 1 with rectal bleeding and stool frequency scores of 0, no mucosal friability, and a > or = 1-point reduction in sigmoidoscopy score at week 8
Lichtenstein et al.[32]	2007	280	MMX mesalamine 2.4 g/day given twice daily or 4.8 g/day given once daily or placebo	Modified UCDAI of 4–10, with a sigmoidoscopy score ≥1 and a PGA score ≤2	Clinical and endoscopic remission (modified UCDAI score of < or = 1, with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction in sigmoidoscopy score) at week 8
Cortot et al.[33]	2008	375	Mesalamine foam or mesalamine enema	CAI for components 1–4 ≥4	Clinical remission at week 4 defined as CAI 1–4 < or = 2
Lichtenstein et al.[34]	2008	517	MMX mesalazine 2.4 g/day or 4.8 g/day or placebo	UCDAI score of 4–10 with a sigmoidoscopy score ≥1 and a PGA score ≤2	Clinical and endoscopic remission at week 8 defined as a total modified UCDAI score of ≤1, calculated as: scores of 0 for rectal bleeding and stool frequency, a combined PGA score and sigmoidoscopy score of ≤1, no mucosal friability and, at least, a one-point reduction from baseline in the sigmoidoscopy score
Kruis et al.[35]	2009	380	3 g OD or 1 g TID mesalazine granules	CAI >4 and EI ≥4	Clinical remission (CAI < or = 4) at week 8
Sandborn et al.[36]	2009	772	Mesalamine 4.8 g/day or 2.4 g/day	PGA equal to 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	Overall improvement at week 6, defined as improvement in the PGA with no worsening in any individual clinical assessment

TABLE 2 (Continued)

First author	Year	Number of patients	Study arms	Definition of mild to moderate ulcerative colitis (inclusion criterion)	Primary endpoint
Scherl et al.[37]	2009	249	3.3 g of balsalazide or placebo tablets twice daily	MMDAI score between 6 and 10, inclusive, with an individual subscale score ≥2 for rectal bleeding and mucosal appearance	Clinical improvement (> or = 3 point improvement in MMDAI) and improvement in rectal bleeding (> or = 1 point improvement) at week 8
Andus et al.[38]	2010	354	Mesalamine 1 g suppository at bedtime or one mesalamine 0.5 g suppository thrice daily	DAI between 3 and 11	Remission at week 6 defined as DAI <4
D'Haens et al.[39]	2010	36	Budesonide-MMX 9 mg tablets or placebo	CAI <14	Clinical improvement (meaning either remission, defined as a CAI ≤4 or a CAI reduction by at least 50% of the baseline value) at week 4
Hartmann et al.[40]	2010	237	Budesonide or mesalazine enemas	CAI >4 and EI >2	Clinical remission at week 4 defined as CAI <4
Ito et al.[41]	2010	225	Mesalamine 2.4 g/day or 3.6 g/day	UCDAI of 3–8 and a bloody stool score of 1 or greater	Decrease in UCDAI at week 8
Gross et al.[42]	2011	343	9 mg budesonide or 3 g mesalazine	CAI ≥6 and EI ≥4	Clinical remission at week 8 defined as CAI ≤4 with stool frequency and rectal bleeding subscores of "0"
Hiwatashi et al.[43]	2011	123	4 g/day mesalazine or 2.25 g/day	UCDAI score of 6–8 points	Improvement in all 4 UCDAI variables (stool frequency, rectal bleeding, mucosal appearance, and physician's overall assessment of disease) at week 8
Lamet et al.[44]	2011	99	Mesalamine 1 g suppository administered QHS or 500 mg suppository administered BID	DAI between 4 and 11	Decrease of DAI at week 6
Sandborn et al.[45]	2012	509	Budesonide MMX (9 mg or 6 mg) or mesalamine or placebo	UCDAI score of 4–10 points	Remission at week 8 defined as combined clinical and endoscopic remission with a UCDAI score ≤1 point, with subscores of 0 for both rectal bleeding and stool frequency, no mucosal friability on colonoscopy, and a ≥1-point reduction from baseline in the endoscopic index score
Flourié et al.[46]	2013	206	Mesalazine (4 g/day) either OD or BD	UCDAI score of 3–8	Clinical and endoscopic remission at week 8 defined as UCDAI score ≤1
Watanabe et al.[47]	2013	129	1 g mesalazine or placebo suppository	UCDAI score between 4 and 8	Endoscopic remission (mucosal score of 0 or 1) at week 4
Probert et al.[48]	2014	127	Oral mesalazine 4 g/day, plus 1 g mesalazine enema or placebo enema	UCDAI score ≥3 and ≤8	Remission at week 4 defined as UCDAI <2
Travis et al.[49]	2014	410	Budesonide MMX 9 mg or 6 mg, or Entocort EC 9 mg or placebo	UCDAI score ≥4 and ≤10	Combined clinical and endoscopic remission, defined as UCDAI ≤1 with a score of 0 for rectal bleeding and stool frequency, no mucosal friability on colonoscopy, and a ≥1-point reduction in endoscopic index score at week 8

TABLE 2 (Continued)

First author	Year	Number of patients	Study arms	Definition of mild to moderate ulcerative colitis (inclusion criterion)	Primary endpoint
Sandborn et al.[50]	2015	546	Budesonide foam or placebo	MMDAI between 5 and 10, inclusive, with subscale ratings of ≥2 for endoscopic appearance and rectal bleeding	Remission at week 6 defined as an endoscopy subscore ≤1, rectal bleeding subscore of 0, and improvement or no change from baseline in the stool frequency subscore of the Mayo score
Sandborn et al.[51]	2015	672	Budesonide MMX 9 mg or budesonide MMX 6 mg or placebo	UCDAI score between 4 and 10	Combined clinical and colonoscopic remission at week 8 defined as a UCDAI ≤1, with no rectal bleeding (UCDAI subscore = 0), normal stool frequency (UCDAI subscore = 0), normal mucosa with no evidence of friability at full colonoscopy and an endoscopic index score ≥1 point lower than baseline
Bosworth et al.[52]	2016	546	Budesonide foam or placebo	MMDAI score ≥5 but ≤10, with subscale ratings ≥2 for rectal bleeding and endoscopic appearance	Remission at week 6 defined as MMDAI endoscopy subscale score ≤1, MMDAI rectal bleeding subscale score 0, and improvement or no change from baseline in MMDAI stool frequency subscale score
D'Haens et al.[53]	2017	817	3.2 g of oral mesalazine, administered as two 1600 mg tablets once, or four 400 mg tablets twice daily	MCS ≥5, a rectal bleeding subscore ≥1, and a MCES score ≥2	Clinical and endoscopic remission at week 8 defined as stool frequency and rectal bleeding subscores of 0 and MCS ≤2 with no individual subscore >1
Rubin et al.[54]	2017	458	Budesonide multimatrix 9 mg or placebo	UCDAI ≥4 and ≤10, mucosal appearance subscore ≥1, and physician's rating of disease activity score of 1 or 2	Combined clinical and endoscopic remission at week 8 defined as total UCDAI score ≤1, with subscale scores of 0 for rectal bleeding, stool frequency, and mucosal appearance
Dignass et al.[55]	2018	306	One 1000 mg mesalazine tablet or two registered 500 mg mesalazine tablets, both taken three times daily	CAI >4 and ≤12 and EI of 4 or greater	Clinical remission at week 8 defined as CAI ≤4, with stool frequency and rectal bleeding subscores of 0
Kruis et al.[56]	2019	337	Budesonide suppositories (2 mg BUS) or 4 mg BUS or 1 g mesalamine suppositories or the combination of 2 mg BUS and 1 g MES	Modified UCDAI 4–10 with an endoscopic subscore of ≥1	Time to resolution of clinical symptoms, defined as the first of 3 consecutive days with a score of 0 for rectal bleeding and stool frequency

Abbreviations: BID, twice a day; CAI, Clinical Activity Index; DAI, Disease Activity Index; EI, Endoscopic Index; MCES, Mayo Clinic Endoscopic Subscale; MCS, Mayo Clinic Score; MES, Mayo endoscopic score; MMDAI, Modified Mayo Disease Activity Index; MMX, multimatrix system; PFA, Patient's Functional Assessment; PGA, Physician's Global Assessment; QHS, every bedtime; UCDAI, Ulcerative Colitis Disease Activity Index.

between 3 and 9 and an endoscopic score ranging from 1 to 2 (1 study,[28] 20%), between 3 and 11 (1 study,[38] 20%), between 4 and 10 (1 study,[27] 20%) and between 3 and 10 (1 study,[22] 20%).

The Modified Mayo Disease Activity Index (MMDAI) was used in 3 studies (7.7%).[37,50,52] Two different MMDAI cut-offs were used to defined mild to moderate active UC: between 5 and 10, inclusive,

with subscale ratings of ≥2 for endoscopic appearance and rectal bleeding (2 studies,[50,52] 66.7%), and between 6 and 10, inclusive, with subscale ratings of ≥2 for endoscopic appearance and rectal bleeding (1 study,[37] 33.3%).

The PGA alone was used in 3 studies (7.7%).[23,30,36] Two different PGA cut-offs ware used to define mild to moderate active UC: PGA

TABLE 3 Ulcerative colitis (UC) disease activity assessment indices

Index name	Abbreviation	Range	Variables
Clinical activity index	CAI	0–29	Number of stools
			Blood in stools
			Investigator's global assessment of symptomatic state
			Abdominal pain or cramps
			Temperature due to colitis
			Extraintestinal manifestations
			Laboratory findings (erythrocyte sedimentation rate, hemoglobin)
Disease activity index	DAI	0–12	Stool frequency
			Rectal bleeding
			Mucosal appearance
			Physician's rating of disease activity
Endoscopic index	EI	0–12	Granulation scattering reflected light
			Vascular pattern
			Vulnerability of mucosa
			Mucosal damage (mucus, fibrin, exsudates, erosions, ulcer)
Mayo clinic score	MCS	0–12	Stool frequency
			Rectal bleeding
			Findings of flexible proctosigmoidoscopy
			Physician's global assessment
Modified Mayo disease activity index	MMDAI	0–12	Bowel frequency
			Rectal bleeding
			Physician's global assessment
			Endoscopy/sigmoidoscopy finding
Ulcerative colitis disease activity index	UCDAI	0–12	Stool frequency
			Rectal bleeding
			Mucosal appearance
			Physician's rating of disease activity

score of 1 or 2 (2 studies,[23,30] 66.7%), and a PGA equal to 2 points (1 study,[36] 33.3%).

The MCS was used in one study (2.6%).[53] Mild to moderate active UC was defined as MCS ≥5, a rectal bleeding subscore ≥1, and a Mayo Clinic Endoscopic Subscale score ≥2.

Predictive factors of response to treatment

Eleven randomized controlled trials (28.2%) reported predictive factors of response to treatment (Table 4).[22–24,29,30,35,36,38,41,49,56] Most studies investigated the efficacy of 5-ASA (10 studies, 90.9%),[22–24,29,30,35,36,38,41,56] while budesonide was assessed in one study (9.1%).[49] The most frequently reported predictor was a mild disease activity (4 studies, 36.4%).[24,35,38,56] Other predictive factors were moderate disease activity (3 studies, 27.3%),[22,30,41] previous treatment with steroids (3 studies, 27.3%),[23,30,36] no extraintestinal

manifestation (2 studies, 18.2%),[24,38] shorter disease duration (1 study, 9.1%),[29] proctitis (1 study, 9.1%),[41] distal disease (1 study, 9.1%),[35] female (1 study,[38] 9.1%), male (1 study, 9.1%),[49] Eastern European patients (1 study, 9.1%),[49] younger patients (1 study, 9.1%),[49] and previous treatment with oral mesalamine or rectal therapies (1 study, 9.1%).[36]

One study (2.6%) reported predictive factors of treatment failure[53]: younger age, higher endoscopic disease activity, higher histopathologic disease activity, and higher leucocyte concentration.

DISCUSSION

During the last 2 decades, various scores have been used to evaluate disease activity in mild to moderate UC. In this systematic review we summarized evidence from 39 randomized controlled trials assessing 5-ASA and/or budesonide, reporting the definition of mild to

TABLE 4 Predictors of good response to treatment in mild to moderate active ulcerative colitis (UC)

First author	Year	Number of patients	Study arms	Definition of mild to moderate UC (inclusion criterion)	Predictive factors of response
Pokrotnieks et al.[18]	2000	111	Mesalazine foam enema or placebo enema	CAI >4 and EI of ≥4	ND
Farup et al.[19]	2001	227	Mesalazine 4g daily given as prolonged-release granules in packets of 1g or prolonged-release tablets of 0.5 g	UCDAI between 3–5 and 6–8	ND
Vecchi et al.[20]	2001	67	Mesalazine 4g orally plus placebo enema, or mesalazine 2g orally plus mesalazine 2g enema	CAI from 4 to 12	ND
Raedler et al.[21]	2004	362	Mesalazine micropellets or tablets	CAI for components 1–4 ≥4 and EI ≥4	ND
Gionchetti et al.[22]	2005	217	Beclomethasone dipropionate 3 mg enema o.d. or mesalamine enema daily	DAI ≥3 and ≤10	Moderate disease
Hanauer et al.[23]	2005	386	Mesalamine 2.4 g/day or 4.8 g/day	PGA of 1 or 2	Previous treatment with steroids
Marakhouski et al.[24]	2005	233	1.5 g mesalazine pellets or tablets	CAI of 6–12 and EI ≥4	Mild disease activity No extraintestinal manifestation
Marteau et al.[25]	2005	127	Mesalazine enema or placebo	UCDAI score ≥3 and ≤8	ND
D'Haens et al.[26]	2006	38	MMX mesalazine 1.2 or 2.4 or 4.8 g/day	UCDAI score of 4–10 with a sigmoidoscopy score of ≥1 and a PGA score of ≤2	ND
Miner et al.[27]	2006	159	Enema of 120 mg alicaforsen or 240 mg alicaforsen or 4g mesalazine	DAI of 4–10	ND
Biancone et al.[28]	2007	92	Beclomethasone diproprionate enema or foam or mesalazine enema or foam	DAI ranging from 3 to 9, and an endoscopic score ranging from 1 to 2	ND
Eliakim et al.[29]	2007	330	Low-volume or high-volume 5-aminosalicylic acid foam	CAI >4 and EI ≥4	Shorter disease duration (<5 years)
Hanauer et al.[30]	2007	301	Oral mesalamine 2.4 g/day or 4.8 g/day	PGA score of 1 or 2	Moderate disease Previous treatment with steroids
Kamm et al.[31]	2007	343	MMX mesalamine 2.4 g/day or 4.8 g/day, or ASACOL 2.4 g/day or placebo	Modified UCDAI score of 4–10 with a sigmoidoscopy score ≥1 and a PGA score ≤2	ND
Lichtenstein et al.[32]	2007	280	MMX mesalamine 2.4 g/day given twice daily or 4.8 g/day given once daily or placebo	Modified UCDAI of 4–10, with a sigmoidoscopy score ≥1 and a PGA score ≤2	ND
Cortot et al.[33]	2008	375	Mesalamine foam or mesalamine enema	CAI for components 1–4 ≥4	ND
Lichtenstein et al.[34]	2008	517	MMX mesalazine 2.4 g/day or 4.8 g/day or placebo	UCDAI score of 4–10 with a sigmoidoscopy score ≥1 and a PGA score ≤2	ND
Kruis et al.[35]	2009	380	3g OD or 1g TID mesalazine granules	CAI >4 and EI ≥4	Mild disease Distal disease

TABLE 4 (Continued)

First author	Year	Number of patients	Study arms	Definition of mild to moderate UC (inclusion criterion)	Predictive factors of response
Sandborn et al.[36]	2009	772	Mesalamine 4.8 g/day or 2.4 g/day	PGA equal to 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	Previous treatment with steroids, oral mesalamine, rectal therapies
Scherl et al.[37]	2009	249	3.3 g of balsalazide or placebo tablets twice daily	MMDAI score between 6 and 10, inclusive, with an individual subscale score ≥2 for rectal bleeding and mucosal appearance	ND
Andus et al.[38]	2010	354	Mesalamine 1g suppository at bedtime or one mesalamine 0.5 g suppository thrice daily	DAI between 3 and 11	Female Mild disease No extraintestinal manifestation
D'Haens et al.[39]	2010	36	Budesonide-MMX 9 mg tablets or placebo	CAI <14	ND
Hartmann et al.[40]	2010	237	Budesonide or mesalazine enemas	CAI >4 and EI >2	ND
Ito et al.[41]	2010	225	Mesalamine 2.4 g/day or 3.6 g/day	UCDAI of 3–8 and a bloody stool score of 1 or greater	Proctitis Moderate disease
Gross et al.[42]	2011	343	9mg budesonide or 3g mesalazine	CAI ≥6 and EI ≥4	ND
Hiwatashi et al.[43]	2011	123	4g/day mesalazine or 2.25 g/day	UCDAI score of 6–8 points	ND
Lamet et al.[44]	2011	99	Mesalamine 1g suppository administered QHS or 500 mg suppository administered BID	DAI between 4 and 11	ND
Sandborn et al.[45]	2012	509	Budesonide MMX (9 mg or 6 mg) or mesalamine or placebo	UCDAI score of 4–10 points	ND
Flourié et al.[46]	2013	206	Mesalazine (4 g/day) either OD or BD	UCDAI score of 3–8	ND
Watanabe et al.[47]	2013	129	1g mesalazine or placebo suppository	UCDAI score between 4 and 8	ND
Probert et al.[48]	2014	127	Oral mesalazine 4 g/day, plus 1g mesalazine enema or placebo enema	UCDAI score ≥3 and ≤8	ND
Travis et al.[49]	2014	410	Budesonide MMX 9 mg or 6 mg, or Entocort EC 9 mg or placebo	UCDAI score ≥4 and ≤10	Younger patients (aged ≤43.5 years) Men Eastern European patients
Sandborn et al.[50]	2015	546	Budesonide foam or placebo	MMDAI between 5 and 10, inclusive, with subscale ratings of ≥2 for endoscopic appearance and rectal bleeding	ND
Sandborn et al.[51]	2015	672	Budesonide MMX 9 mg or budesonide MMX 6 mg or placebo	UCDAI score between 4 and 10	ND

(Continues)

TABLE 4 (Continued)

First author	Year	Number of patients	Study arms	Definition of mild to moderate UC (inclusion criterion)	Predictive factors of response
Bosworth et al.[52]	2016	546	Budesonide foam or placebo	MMDAI score ≥5 but ≤10, with subscale ratings ≥2 for rectal bleeding and endoscopic appearance	ND
D'Haens et al.[53]	2017	817	3.2 g of oral mesalazine, administered as two 1600 mg tablets once, or four 400 mg tablets twice daily	MCS ≥5, a rectal bleeding subscore ≥1, and a MCES score ≥2	Treatment failure: Younger age; Higher endoscopic disease activity; Higher histopathologic disease activity; Higher leucocyte concentration
Rubin et al.[54]	2017	458	Budesonide multimatrix 9 mg or placebo	UCDAI ≥4 and ≤10, mucosal appearance subscore ≥1, and physician's rating of disease activity score of 1 or 2	ND
Dignass et al.[55]	2018	306	One 1000 mg mesalazine tablet or two registered 500 mg mesalazine tablets, both taken three times daily	CAI >4 and ≤12 and EI of 4 or greater	ND
Kruis et al.[56]	2019	337	Budesonide suppositories (2 mg BUS) or 4 mg BUS or 1g mesalamine suppositories or the combination of 2 mg BUS and 1 g MES	Modified UCDAI 4–10 with an endoscopic subscore of ≥1	Mild disease

Abbreviations: BID, twice a day; CAI, Clinical Activity Index; DAI, Disease Activity Index; EI, Endoscopic Index; MCES, Mayo Clinic Endoscopic Subscale; MCS, Mayo Clinic Score; MES, Mayo endoscopic score; MMDAI, Modified Mayo Disease Activity Index; MMX, multimatrix system; ND, non disponible; PGA, Physician's Global Assessment; QHS, every bedtime; TID, three times a day; UCDAI, Ulcerative Colitis Disease Activity Index.

moderate active UC. Six different scores were used to define mild to moderate active UC, highlighting relevant heterogeneity in the literature. The UCDAI was the most adopted score with a value between 4 and 10 as a threshold to indicate mild to moderate disease. This composite index includes a rectal bleeding score (RBS), a stool frequency subscore (SFS), endoscopic appearance, and physician global assessment. In contrast, mild to moderate active UC was defined using the MCS in only one study in our review.

Recently, a similar systematic review by Sedano and colleagues investigated the definition of mild to moderate UC using data from ClinicalTrials.gov.[57] A total of 61 ongoing studies were included (38 (62%) placebo-controlled studies, 11 (18%) active comparator controlled, and 11 (18%) uncontrolled). Of note, the MCS was the most frequently used score (50/61, 82%) while the UCDAI was detected only in a small percentage of cases (8/61, 13.1%). The authors proposed a definition of mild to moderate active UC based on the MCS: MCS of 4-9 using Mayo endoscopic score (MES) ≥2 in combination with RBS ≥1, and SFS ≥1 or MES ≥1 and Geboes score >2B.0 or Robarts Histopathology Index ≥10 and/or feacal calprotectin >250 µg/g.[57] Probably these contrasting data are associated to the considered study period. We considered studies conducted in the last 20 years, while Sedano et al. considered ongoing studies. Furthermore, the MCS is easy to use and is commonly used in clinical practice.

Regulatory authorities have highlighted the limitations of the MCS and UCDAI.[58] One of the major limitations is the PGA subscore.[58] This single general item cannot adequately capture whether benefit is achieved in the important signs and symptoms, and it not derived directly from the patient.[58] Accordingly, the PGA subscore should not be used to assess disease activity.[58]

In our systematic review, we also investigated predictive factors of response to treatment with 5-ASA or budesonide in mild to moderate active UC. Only one third of the included studies reported predictive factors of response to treatment. Mild and moderate disease activity, previous treatment with steroids, no extraintestinal manifestation, shorter disease duration, and distal disease were reported as predictive factors of response to treatment.

To the best of our knowledge, this is the first systematic review of randomized controlled trials describing the definition of mild to moderate UC and predictive factors of response to treatment, focusing only on 5-ASA and budesonide. In addition, other strength of our article is the high quality of the included studies as demonstrated

by the rate of studies with a Jadad score greater than 3. However, some limitations need to be pointed out. In fact, the included studies are very heterogeneous. This is partly explained by the considerable time span between studies and the lack of commonly accepted guidelines on this topic. Almost all recent randomized controlled trials focus on use of biologics of small molecules in patients with moderately to severely active UC, for which regulatory guidance has recommended appropriate efficacy assessments, endpoint definitions, and timing to measure these outcomes.[57,58] However there is no consensus definition for mild to moderate disease activity resulting in heterogeneous study populations.[57,59] The heterogeneity of available studies in the selection of patients suggest that the development of an international consensus on the definition of mild to moderate active UC used for inclusion of patients in clinical trials would be useful to allow harmonization. Other symptoms, such as faecal urgency for example, might be interesting to include in the definition of mild to moderate active UC.

In conclusion, this review found substantial heterogeneity in the scoring indexes used and their definitions of mild to moderate active UC. Similar definition of mild to moderate active UC should be considered to minimize heterogeneity and ensure validity of future randomized controlled trials. The definition of mild to moderate active UC should combine clinic and endoscopic evaluation, in line with the current trend of making evaluations more objective and standardized.

AUTHOR CONTRIBUTIONS

Silvio Danese and Laurent Peyrin-Biroulet conceived the study. Bénédicte Caron wrote the article and created tables and figures. Vipul Jairath, Ferdinando D'Amico, Kristine Paridaens, Fernando Magro, Silvio Danese, and Laurent Peyrin-Biroulet critically reviewed the content of the paper and supervised the project. The manuscript was approved by all authors.

CONFLICT OF INTEREST

B Caron reports lecture and/or consulting fees from Abbvie, Amgen, Celltrion, Janssen, Ferring, Takeda. V Jairath reports consulting/advisory board fees from AbbVie, Alimentiv Inc (formerly Robarts Clinical Trials), Arena pharmaceuticals, Asahi Kasei Pharma, Asieris, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Reistone Biopharma, Roche, Sandoz, Second Genome, Takeda, Teva, Topivert, Vividion; speaker's fees from, Abbvie, Ferring, Galapagos, Janssen Pfizer Shire, Takeda, Fresenius Kabi. F D'Amico declares no conflict of interest. K Paridaens is an employee of Ferring Pharmaceuticals. F Magro received a fee for presenting from: AbbVie, Ferring, Falk, Hospira, PharmaKern, MSD, Schering, Laboratórios Vitoria, Vifor Pharma, OM Pharma. S Danese has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson and Johnson, Millenium Takeda, MSD, Nikkiso Europe GmbH, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma and Vifor. L Peyrin-Biroulet reports personal fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Celltrion, Takeda, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Inotrem, Allergan, MSD, Roche, Arena, Gilead, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, OSE Immunotherapeutics, Enthera, Theravance, Pandion Therapeutics, Gossamer Bio, Viatris, Thermo Fisher; grants from Abbvie, MSD, Takeda, Fresenius Kabi; stock options: CTMA.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.