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INFLAMMATORY BOWEL DISEASE

An International Consensus on Appropriate Management of Corticosteroids in Clinical Trials in Inflammatory Bowel Disease

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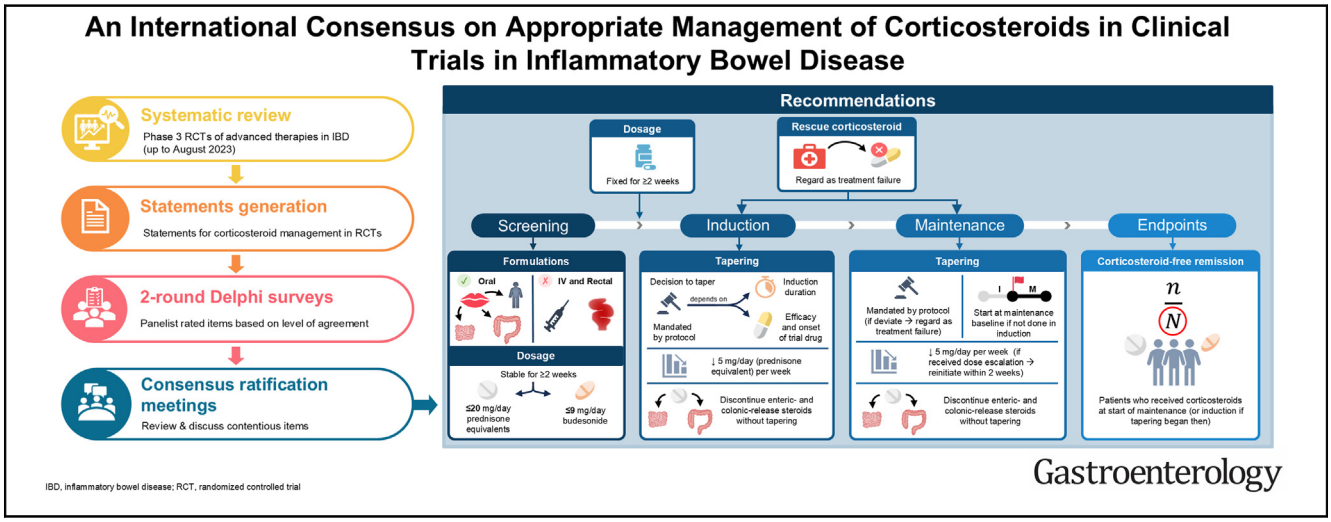

See editorial on page 1119.

BACKGROUND & AIMS: Approval of new therapies for inflammatory bowel disease (IBD) requires rigorously designed and well-executed randomized controlled trials (RCTs). Corticosteroids remain a cornerstone of IBD induction therapy, and many patients in trials are enrolled while taking corticosteroids. Despite this, approaches to corticosteroid management in RCTs have been highly heterogeneous, often differing from clinical practice. This negatively impacts patients' willingness to participate due to prolonged corticosteroid exposure and may potentially bias outcomes in the clinical trial. Our aim is to provide comprehensive standardized recommendations on key aspects of corticosteroid use in IBD clinical trials through a multiphase, international expert consensus, with a goal to help inform and standardize practice in future RCTs. **METHODS:** The consensus was informed by a systematic review of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials, which determined the corticosteroid management rules used in placebo-controlled trials of advanced therapies in IBD. International expert consensus recommendations for all aspects of corticosteroid management in RCTs were then developed using a modified Delphi process with 2 rounds of survey questions and a ratification meeting. **RESULTS:** These recommendations propose management of corticosteroids during screening, induction, and maintenance phases of pharmacologic trials in IBD and define corticosteroid-related end points. We emphasize the need for minimizing corticosteroid exposure through expedited tapering and shorter fixed-dosing periods that more closely reflect clinical care and provide recommendations for standardized definitions of corticosteroid-free remission. **CONCLUSIONS:** These recommendations will serve to optimize trial design and facilitate appropriate, acceptable, and standardized RCT corticosteroid handling practices.

Keywords: Crohn's Disease; Steroids; Ulcerative Colitis; Delphi.

The approval of novel therapies for inflammatory bowel disease (IBD) relies on rigorously designed and well-executed randomized controlled trials (RCTs). Over the past decade, several advances in RCT design for moderately-to-severely active Crohn's disease (CD) and ulcerative colitis (UC) have been implemented, including more stringent qualification of eligible patients at enrollment and better standardization of what, how, and when to measure key efficacy and safety outcomes.[1] An area of RCT design that continues to evolve is the management of concomitant medications, and in particular, the handling of baseline corticosteroids, which has come under increasing scrutiny. Corticosteroids remain a cornerstone of treatment for the acute management of IBD in routine care, resulting in many patients entering trials on corticosteroids.[2] Despite their efficacy for improving symptoms, corticosteroid use is associated with a well-established adverse effect profile, which can obscure evaluating risk profiles for novel therapies,[2] and avoiding prolonged and excessive corticosteroid exposure is an important long-term goal.[3]

Approaches to corticosteroid management in RCTs have been highly heterogeneous. Across studies, there are differences on the maximum allowable dose at study entry, permitted corticosteroid formulations, tapering regimens according to dosage and timing that may be protocol-defined or driven by investigator discretion, allowance for rescue dosing in maintenance, timing of end point assessment, and even the definition of corticosteroid-free remission.[4] Historically, clinical trial protocols for corticosteroid management have differed from clinical care and can negatively impact the willingness of patients to participate in RCTs. For example, most studies have required patients to receive stable doses of corticosteroids for several weeks before enrollment and then maintain fixed doses during

Abbreviations used in this paper: CD, Crohn's disease; IBD, inflammatory bowel disease; RCT, randomized controlled trial; UC, ulcerative colitis.

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Lack of corticosteroid handling consistency in randomized controlled trials for inflammatory bowel diseases has resulted in differences in corticosteroid exposure among participants, impacting trial interpretation and generalizability to clinical care.

NEW FINDINGS

This is the first international expert consensus providing recommendations for appropriate corticosteroid use in randomized controlled inflammatory bowel disease trials, with emphasis on minimizing corticosteroid exposure through expedited tapering and shorter periods of fixed dosing, more closely resembling clinical care.

LIMITATIONS

The scope and recommendations apply only to drug trials with adult patients with moderate-to-severe inflammatory bowel disease and not necessarily nondrug trials, specific phenotypes of inflammatory bowel disease, and pediatric patients.

CLINICAL RESEARCH RELEVANCE

This first set of internationally guided recommendations for corticosteroid management in randomized controlled trials has been developed to improve trial design optimization for adult patients with inflammatory bowel disease. These recommendations will serve to potentially facilitate more appropriate, acceptable, and uniform corticosteroid handling in randomized controlled trials, maximizing comparability between trials, and minimizing steroid-related harm.

BASIC RESEARCH RELEVANCE

Standardizing the appropriate management of concomitant corticosteroids is a major research priority for the field of inflammatory bowel disease to improve the conduct and interpretability of randomized controlled trials for both health care providers and patients.

induction, resulting in extended corticosteroid exposure.[5–9] Concomitant corticosteroid use has been shown to be associated with higher rates of clinical remission in the placebo arm.[10] Only recently, trials have used early tapering of corticosteroids after starting a novel therapy during induction.[11] Moreover, although corticosteroid-free outcomes are of both clinical and regulatory relevance, corticosteroid handling practices can directly affect the interpretation of trial end points by masking symptoms of active disease or increasing the risk of adverse events occurring during trials.

Divergent practices between treatment arms may confound corticosteroid-related trial outcomes.[12] More specifically, a systematic review showed that rates of corticosteroid-free clinical remission are ∼20% to 25% lower than rates of overall clinical remission.[4] This end point was also less likely to reach statistical significance—both due to its stringency and lack of statistical power. Furthermore, patients in trials with corticosteroid tapering regimens left to the discretion of the clinician were more likely to achieve clinical remission at 1 year but less likely to achieve corticosteroid-free clinical remission than patients in trials with protocol-mandated tapering regimens.[13]

Given this substantial heterogeneity in corticosteroid management practices and potential impact on participant enrollment, trial conduct, and interpretation of study results, we aimed to provide comprehensive standardized recommendations on key aspects of corticosteroid use in IBD RCTs through a multiple phase, international expert consensus, with a goal to help inform and standardize practice globally in future RCTs.

Methods

Overview

The scope of this multiple phase consensus exercise is to inform corticosteroid management practices in RCTs of pharmacologic therapies for adult patients (≥18 years) with moderately-to-severely active CD and UC. This guidance does not consider trials of surgical interventions or specific disease phenotypes, such as acute severe UC, pouchitis, or perianal fistulizing CD, recognizing that these patients may have different considerations for when and how corticosteroids are used.

Statement Generation

A systematic review on the handling of corticosteroids in RCTs served as the basis for statement generation, using MEDLINE, EMBASE, and the Cochrane CENTRAL Register of Controlled Trials.[4] The search was updated to 2023, and the review was expanded by searching the protocols of all phase 3 RCTs of currently approved advanced IBD therapies (Supplementary Material and Supplementary Figure 1). Corticosteroid management practices were divided in several domains: (1) corticosteroid management during screening, (2) corticosteroid management during induction, (3) corticosteroid management during maintenance, and (4) corticosteroid-related end points. These domains were selected because they describe the key stages of an RCT in IBD and are directly reflected in clinical trial protocols. Information extracted from the publications included permitted corticosteroid formulations, maximum permitted prerandomization corticosteroid dose, duration of stable prerandomization corticosteroid dose, duration of fixed corticosteroid dosing, the onset and timing of corticosteroid tapering, rate of corticosteroid tapering, protocol-defined vs investigator-defined corticosteroid tapering regimen, allowance for rescue corticosteroid courses after tapering, and definitions of corticosteroid-free remission.

Panelist Selection

A diverse pool of gastroenterologists, methodologists, and clinical trialists with clinical knowledge, RCT-related experience, and geographic diversity was identified and invited to participate based on a prior consensus initiative.[1] Requirements for participation, identical as in a prior initiative, included (1) expertise in IBD trial conduct or outcome assessment, or both, as reflected by metrics such as authorship of ≥25 publications related to IBD, or involvement in ≥2 IBD clinical trials as an investigator, or through input into the trial

design; or (2) clinical expertise as demonstrated by being the medical lead of a dedicated IBD center. Stringent criteria were set for panelist eligibility because the panel was asked to critically examine highly technical considerations around clinical trial design, conduct, and interpretation. Given the academic nature of this initiative, industry representatives were not invited to avoid any real or perceived conflicts of interest. The final list of panelists was confirmed by the study steering committee (J.H., B.G.F., V.J., and C.M.), who also had voting rights in the Delphi process.

Delphi Process

An exhaustive list of statements generated through the systematic review process was incorporated in a 2-round Delphi survey and e-mailed to the panelists (May and September 2023). The Delphi method permits panelists to anonymously reach consensus through iterative rounds of sequential questionnaires.[14] Panelists were asked to rate each item on a Likert scale from 1 to 9 to indicate their level of agreement: "strongly agree" (7–9), "uncertain" (4–6), and "strongly disagree" (1–3). Items had free-text entry options for panelists to provide clarifying statements or add further items of interest for inclusion in subsequent rounds of voting. Panelists received a summary of the systematic review on corticosteroid management practices in RCTs as a supplement to the survey (Supplementary Table 1). Responses were collated, and descriptive statistics were used to summarize the scoring and distribution of the entire panel. After each round of voting, results were provided to panelists in a feedback summary.

Items for which $\geq$80% of panelists scored in the 7 to 9 range and $<$15% of panelists scored in the 1 to 3 range during the first or second round of voting were decided a priori to have met consensus and were not voted upon further, with a similar rule used to exclude items with strong disagreement.

Two consensus ratification meetings were held by videoconference in March 2024. Criteria for consensus were reviewed at each meeting. Items not having reached consensus for inclusion or exclusion in prior rounds were reviewed and discussed, with a focus on potentially contentious items rated in the 7 to 9 range by 60% to 80% of panelists, and voting was simplified to "agree," "uncertain," and "disagree." Items receiving $\geq$70% of votes for "agree" and $<$15% of votes for "disagree" were ratified for final inclusion; items receiving $\geq$70% of votes for "disagree" and $<$15% of votes for "agree" were ratified for final exclusion.

Patient and Public Involvement

Patients who previously participated in Community, Outreach, Research and Education (CORE)-IBD and who had consented to be contacted for future research were invited to provide feedback on the use of corticosteroids in IBD trials. This was done using an online survey (ethics approval ID: REB25-0009), allowing patients to provide structured and unstructured feedback. The survey was designed to evaluate similar concepts to what was derived in the consensus process, with questions evaluating allowable formulation of corticosteroids and management of corticosteroids during screening, induction, and maintenance. Open-ended responses were also encouraged to allow participants the opportunity to provide additional feedback that was considered important from a patient perspective.

Results

Panelists and Survey Statements

Of the 72 invited experts, 45 participated in the Delphi panel; most panelists practiced in academic hospitals (41 of 45 [91.1%]) as clinician-researchers (38 of 45 [84.4%]) and had $>$20 years of experience (30 of 45 [66.7%]) (Supplementary Table 2). The first-round survey consisted of 140 statements, of which 25 statements reached consensus during the first 2 rounds of voting. In the ratification meeting, panelists discussed and voted on 114 statements. Supplementary Table 3 summarizes all voting results.

Corticosteroid Management During Screening

Allowable corticosteroid formulations during screening. Table 1 summarizes statements reaching consensus on corticosteroid management during screening. The panelists agreed that oral systemic corticosteroids and oral enteric- or colonic-release corticosteroids could be used during screening. In contrast, panelists recommended that there should be temporal limitations on the use of intravenously or rectally administered corticosteroid formulations before and during the screening period. Patients requiring intravenous corticosteroids were generally considered to be too ill to participate in outpatient clinical trials of patients with moderately-to-severely active ambulatory IBD. Acknowledging that exceptions may apply in trials of hospitalized patients with acute severe UC, which was outside the scope of the current consensus, the panelists determined that any use of intravenous corticosteroids during screening should be exclusionary for trial participation. Additionally, transitioning an acutely ill patient treated with intravenous corticosteroids to oral systemic corticosteroids would also likely exceed maximum acceptable baseline doses and could result in excessive prolonged corticosteroid exposure owing to the need for stable dosing before randomization.

The panel agreed that rectally administered corticosteroids should be discontinued $\geq$2 weeks before the baseline visit in both CD and UC. The impact of locally administered corticosteroids on baseline endoscopic activity was recognized to be greater in UC than in CD. The panel discussed that despite a relative paucity of direct empirical evidence on the subject, use of local rectally delivered corticosteroids could attenuate endoscopic disease activity in the distal colon, especially for milder lesions, and thereby confound the interpretation of eligibility upon endoscopy. However, because many patients rely on using rectal corticosteroids for symptom management, especially for urgency, a longer time interval than 2 weeks was agreed to be excessive and impractical, with a potential negative impact on recruitment.

Defining the baseline visit. The panel discussed 2 study configurations, using either the screening endoscopy or date of randomization as the time point for calculating

Table 1. Summary of Statements Reaching Consensus on Corticosteroid Handling During Screening and Before the Screening Endoscopy in Randomized Controlled Trials in Inflammatory Bowel Disease

Corticosteroids during screening and before the screening endoscopy/randomization	Percentage of agreement[a] (%)
Patients with Crohn's disease should be permitted to receive the following corticosteroid formulations at any time during screening:	
• Oral systemic corticosteroids	81.4
• Oral enteric-release corticosteroids	86.0
Patients with ulcerative colitis should be permitted to receive the following corticosteroid formulations at any time during screening:	
• Oral systemic corticosteroids	90.5
• Oral colonic-release corticosteroids	83.7
Patients with Crohn's disease should discontinue rectally administered corticosteroids at least 2 weeks before the screening endoscopy/randomization.	94.4
Patients with ulcerative colitis should discontinue rectally administered corticosteroids at least 2 weeks before the screening endoscopy/randomization.	90.0
Any period of intravenous corticosteroid use during screening should be exclusionary for trial participation.	85.0
Patients who have received oral systemic corticosteroids before the screening endoscopy/randomization should be required to have used a stable dosage for at least 2 weeks.	100.0
Patients who have received oral enteric- or colonic-release corticosteroids before the screening endoscopy/randomization should be required to have used a stable dosage for at least 2 weeks.	100.0
Patients who have received oral systemic corticosteroids before the screening endoscopy/randomization should not be permitted to have exceeded 20 mg of prednisone equivalent per day as the maximum prerandomization dosage.	78.9
Patients who have received budesonide before the screening endoscopy/randomization should not be permitted to have exceeded 9 mg daily as the maximum prerandomization dosage.	94.1

[a]The percentage of agreement is reported from the round of voting when consensus was achieved.

the duration of prior and stable corticosteroid dosing during screening. No consensus was reached, although using the date of randomization was generally preferred. Advantages and disadvantages of both options were reviewed. The panel discussed that even though corticosteroids could improve endoscopic disease activity, which would support designating the screening endoscopy as the baseline visit, the influence of corticosteroids on the patients' symptoms was probably greater. Moreover, the findings at screening endoscopy could subsequently influence the investigator's behavior, which could result in some patients receiving increased corticosteroid dosing after the screening endoscopy. Choosing the date of randomization as the baseline visit was also believed to be more effective at capturing the effect of a novel therapy.

Corticosteroid dosing during screening. The panel discussed that the dominant factors determining the required duration of stable corticosteroid dosing before randomization and the maximal allowable corticosteroid dose during screening were (1) the timing of corticosteroid tapering and (2) the highest allowable dose of corticosteroid exposure. There was consensus that the dosage of oral systemic and enteric- and colonic-release corticosteroids should be stable for $\geq$2 weeks before the baseline visit. The maximum dosage of oral systemic corticosteroids was determined by the panel to be 20 mg/d (in prednisone equivalents, recognizing that different corticosteroid formulations have different relative potency), and the maximum dosage of budesonide was determined to be 9 mg/d. Importantly, these dosages were discussed in the context of historical trial designs requiring patients to remain on a stable, fixed dose of corticosteroids for the entire induction period. The panel discussed that higher doses of oral systemic corticosteroids, up to 30 mg/d prednisone equivalents, could be acceptable if tapering was started during induction.

Corticosteroid Management During Induction

Corticosteroid tapering during induction. Statements reaching consensus on corticosteroid management during screening are summarized in Table 2. The decision to require corticosteroid tapering during induction depends on the duration of the induction trial and the expected efficacy and rapidity of onset of the novel therapy, citing the recent example of upadacitinib in CD.[11] The panelists also noted that considerations for early corticosteroid tapering may differ between phase 2 and phase 3 trials: in the former, fixed dosing during induction may be justified when clinical efficacy and time to response may be unclear. This could be followed by a mandated tapering schedule in induction for the phase 3 trial, informed by efficacy data from earlier stages of clinical development.

In trials incorporating tapering during induction, there was consensus that the decision to taper, the time of onset for tapering, and the rate of tapering should be mandated by the trial protocol and not left to the individual investigator's judgement. There was consensus that the decision of when and how to taper should be uniform across participants of RCTs and that the dosage of systemic oral corticosteroids should be fixed for $\geq$2 weeks after randomization in an induction trial before tapering. The tapering schedule for dosages of 20 mg/d prednisone equivalents should be

Table 2. Summary of Statements Reaching Consensus on Corticosteroid Handling During Induction in Randomized Controlled Trials in Inflammatory Bowel Disease

Corticosteroids during induction	Percentage of agreement[a] (%)
During the induction phase of a trial, the dosage of oral systemic corticosteroids should be fixed for at least 2 weeks after randomization.	78.9
During the induction phase of a trial, the dosage of oral enteric- or colonic-release corticosteroids should be fixed for at least 2 weeks after randomization.	77.8
During the induction phase of a trial, the decision to require tapering the dosage of corticosteroids should depend on the following factors:	
• the duration of the induction trial	88.9
• the expected efficacy of the investigational agent	77.8
• the expected speed of onset of the investigational agent	72.2
During the induction phase of a trial, the dosage of oral systemic corticosteroids should be tapered in patients receiving the same treatment regimen, regardless of an early symptomatic response, to avoid complications in interpreting induction trial results.	93.8
During the induction phase of a trial, the onset of oral systemic corticosteroid tapering should be mandated by the trial protocol.	88.4
During the induction phase of a trial, the rate of oral systemic corticosteroid tapering should be mandated by the trial protocol.	90.7
During the induction phase of a trial, the onset of oral enteric- or colonic-release corticosteroid tapering should be mandated by the trial protocol.	88.4
During the induction phase of a trial, the rate of oral enteric- or colonic-release corticosteroid tapering should be mandated by the trial protocol.	90.7
During the induction phase of a trial, the dosage of oral enteric- or colonic-release corticosteroids should be tapered in patients receiving the same treatment regimen, regardless of an early symptomatic response, to avoid complications in interpreting induction trial results.	93.8
In a trial that requires tapering of corticosteroids during the induction phase, dosages of 20 mg/d prednisone equivalents should be tapered by 5 mg/d per week until discontinuation.	100.0
Enteric- and colonic-release budesonide dosages should be discontinued without tapering during the induction phase.	88.9
Patients starting oral systemic corticosteroids as rescue therapy de novo during induction should be regarded as having failed treatment.	81.4
Patients starting oral enteric- or colonic-release corticosteroids as rescue therapy de novo during induction should be regarded as having failed treatment.	90.2
Patients starting rectally administered corticosteroids as rescue therapy de novo during induction should be regarded as having failed treatment.	100.0
Patients starting intravenous corticosteroids as rescue therapy should be regarded as having failed treatment.	95.3

[a]The percentage of agreement is reported from the round of voting when consensus was achieved.

constant at 5 mg/wk to shorten total corticosteroid exposure for trial participants.

The panelists acknowledged the heterogeneity of tapering regimens in clinical practice. Tapering regimens described in the statements were derived from the systematic review of trial protocols. The panelists cited the clarity and simplicity of a uniform tapering regimen as a key advantage in addition to limiting corticosteroid exposure. In clinical care, some practitioners may choose prolonged tapering schedules (eg, by 2.5 mg/wk) to avoid symptomatic flares or minimize risk of adrenal insufficiency, although data supporting this in IBD are scarce. The panel agreed that enteric- and colonic-release corticosteroids could be discontinued without tapering.

Managing corticosteroid-dependent and refractory patients in induction. Recognizing that RCTs enroll a mix of patients who may be corticosteroid-responsive, -refractory, or -dependent, the panel discussed whether unique practices should be implemented for different patient phenotypes and based on initial

Table 3. Summary of Statements Reaching Consensus on Corticosteroid Handling During Maintenance in Randomized Controlled Trials in Inflammatory Bowel Disease

Corticosteroids during maintenance	Percentage of agreement[a] (%)
The tapering of the oral systemic corticosteroid dosage should be initiated at the beginning of the maintenance phase of a trial (if not already done in induction).	75.6
During the maintenance phase of a trial, the onset of oral systemic corticosteroid tapering should be mandated by the trial protocol.	83.7
During the maintenance phase of a trial, the rate of oral systemic corticosteroid tapering should be mandated by the trial protocol.	83.7
In a trial that requires tapering of corticosteroids during the maintenance phase, dosages of 20 mg/d prednisone equivalents should be tapered by 5 mg/d per week until discontinuation.	78.0
Enteric- and colonic-release budesonide dosages should be discontinued without tapering during the maintenance phase.	93.8
In a trial that requires tapering of corticosteroids during the maintenance phase, patients who received corticosteroid dosage escalation should reinitiate tapering within 2 weeks after dosage escalation.	92.9
Patients who deviated from the recommended oral systemic corticosteroid tapering schedule by receiving dosage escalation in the maintenance phase of a trial should be regarded as having failed treatment.	92.9
Patients who deviated from the recommended oral enteric- or colonic-release corticosteroid tapering schedule by receiving dosage escalation in the maintenance phase of a trial should be regarded as having failed treatment.	85.7
Patients who received oral systemic corticosteroid dosage escalation to the baseline dosage of the maintenance trial during tapering should be regarded as having failed treatment.	85.7
Patients who received oral enteric- or colonic-release corticosteroid dosage escalation to the baseline dosage of the maintenance trial during tapering should be regarded as having failed treatment.	85.7
Only patients who used any formulation of corticosteroids at the start of the maintenance trial (or induction if that is when tapering began) should be used as the denominator for calculating the rate of corticosteroid-free remission.	71.4
Patients should be permitted to transiently receive increased doses of corticosteroids to treat indications beyond inflammatory bowel disease (eg, asthma, adrenocortical insufficiency, stress doses for surgery) for ≤2 weeks.	86.7

[a]The percentage of agreement is reported from the round of voting when consensus was achieved.

symptomatic response. There was agreement that a single protocol would be preferable. First, it was noted that there are divergent definitions of corticosteroid dependency and that it is uncertain whether corticosteroid dependency is an effect modifier of treatment response to a novel therapy. Operationally, it would be challenging to unify the definition of corticosteroid dependency across multiple trial sites and investigators and subsequently implement different tapering regimens for dependent patients.

Second, although it was identified that some patients and investigators may be hesitant to taper corticosteroids during induction in the absence of symptomatic improvement, defining clinical improvements may differ between sites, and enforcing early corticosteroid tapering would minimize placebo responses during induction. There was consensus that any corticosteroid formulation introduced de novo during induction as rescue treatment should be considered a treatment failure.

Corticosteroid Management During Maintenance

Corticosteroid tapering during maintenance. Table 3 summarizes statements reaching consensus on corticosteroid management during maintenance. The panelists agreed that tapering of oral systemic as well as enteric- and colonic-release corticosteroids should be initiated at the start of the maintenance phase if not already done during induction. There was consensus that the onset and rate of tapering of all corticosteroid formulations should be mandated by the trial protocol rather than left to individual investigator discretion. The panelists supported a unified tapering regimen of 5 mg/d prednisone-

equivalent weekly until discontinuation for systemic corticosteroids, irrespective of the starting dose, whereas enteric- and colonic-release corticosteroids could be discontinued without tapering during the maintenance phase.

Requirement for rescue corticosteroids. The panel discussed the role of rescue corticosteroids during the maintenance phase and did not reach consensus on whether escalation of corticosteroid dosing to the maintenance baseline was permissible in the case of worsening symptoms of IBD. Although most patients in maintenance trials have demonstrated response to treatment, the requirement for corticosteroids during maintenance may be an important marker of loss of response. Conversely, it was noted that other patients, particularly those who are treatment experienced, may be well served by continuing in an RCT if their symptoms could be controlled by a short course of rescue corticosteroids. This comes with the caveat that the rescue corticosteroids would be used at a dose no higher than their induction baseline dose and with similar tapering after initiation, as would also be acceptable practice in routine clinical care. The panel agreed that corticosteroids should not be used to prolong trial participation in treatment nonresponders. Accordingly, there was consensus that patients requiring $\geq$1 courses of rescue corticosteroids should be regarded as having failed treatment.

The panel also considered the subgroup of patients who require short courses of corticosteroids for other compelling treatment indications in the absence of an IBD-related flare. For instance, giving corticosteroids to patients for pulmonary indications (eg, asthma or chronic obstructive pulmonary disease) was considered acceptable. In this setting, there was consensus that corticosteroids for other indications should either be stopped or tapered within 2 weeks, depending on the dose.

Corticosteroid-Related End Points

The panelists discussed which denominator should be used for the calculation of corticosteroid-free remission. Overall, the panelists supported using the number of participants using any formulation of corticosteroids at the start of the maintenance phase (or at the start of induction if corticosteroids were tapered during induction). Using all patients entering the maintenance trial as the denominator was considered too liberal because most patients are not receiving concomitant corticosteroids, and this definition would artificially inflate rates of corticosteroid-free remission by including patients who were not exposed to corticosteroids at trial commencement.

The optimum period after corticosteroid withdrawal to define a "corticosteroid-free" state also did not reach consensus. The panelists agreed that longer durations of corticosteroid discontinuation were likely indicative of deeper levels of remission. There was consensus that withdrawal of corticosteroids at the last study visit or within 2 weeks of the last study visit was too brief, and most panelists supported corticosteroid withdrawal for $\geq$12 weeks before the final study visit as the most appropriate, although this definition did not reach the consensus threshold.

Patient Perspectives

Of 40 patients who provided feedback on the management of corticosteroids, 22 (55%) were women, 33 (82.5%) had CD, and 30 of 39 (76.9%) were on an advanced biologic or small molecule therapy (Supplementary Table 4). Some of the 40 patients did not provide responses to all the questions in the online survey. Most patients (59.0% [23 of 39]) had prior adverse effects to corticosteroids, most notably mood disturbance, sleeplessness, weight gain, and fatigue. Approximately two-thirds of patients felt that oral systemic and oral gut-specific therapies should be allowed in clinical trials, and approximately half of patients felt that rectal steroid formulations should also be permitted. Ten patients (25%) felt that corticosteroids should not be permitted in clinical studies, with comments expressing concerns about the risk of corticosteroid-related adverse effects and potential differences in how corticosteroids are prescribed and tolerated between different patients and prescribers. There was uncertainty and disagreement among patients about the maximum allowable dose of prednisone and duration of stable dosing before trial enrollment, although patients generally favored earlier tapering of corticosteroids in both induction and maintenance.

In the comments, patients expressed that the decision to use corticosteroids is highly variable between patients, especially given the adverse effect profile, and therefore, this decision should be individualized by the prescriber based on patient characteristics. Patients generally agreed that clinical trial drugs are unlikely to be working in patients who are unable to taper corticosteroid use due to reappearance of symptoms, and most patients favored longer durations off corticosteroids (even >24 weeks) to truly define corticosteroid-free remission.

Discussion

This international collaborative initiative has led to the development of the first comprehensive consensus-based recommendations for the appropriate management of concomitant corticosteroids in RCTs of pharmacologic therapies for the treatment of IBD (Figure 1). Unified corticosteroid management practices in RCTs are critical to ensure comparability between trials, minimize risk of excessive corticosteroid exposure as a result of trial design and eligibility criteria, and minimize potential confounding effects of heterogeneous steroid tapering regimes on trial end points.

Recruitment rates in IBD RCTs have decreased substantially in recent years.[15] There are multiple reasons for this trend; however, the need for prolonged corticosteroid exposure, often longer than in routine care, was identified as one of the barriers to trial participation by patients.[16] The requirement for a washout period between discontinuing a prior advanced therapy and entering an RCT is a contributing factor to increased corticosteroid use[17] because patients are often bridged with corticosteroids, even in the absence of empirical evidence that washout periods are needed. Exposure to corticosteroids is further prolonged by

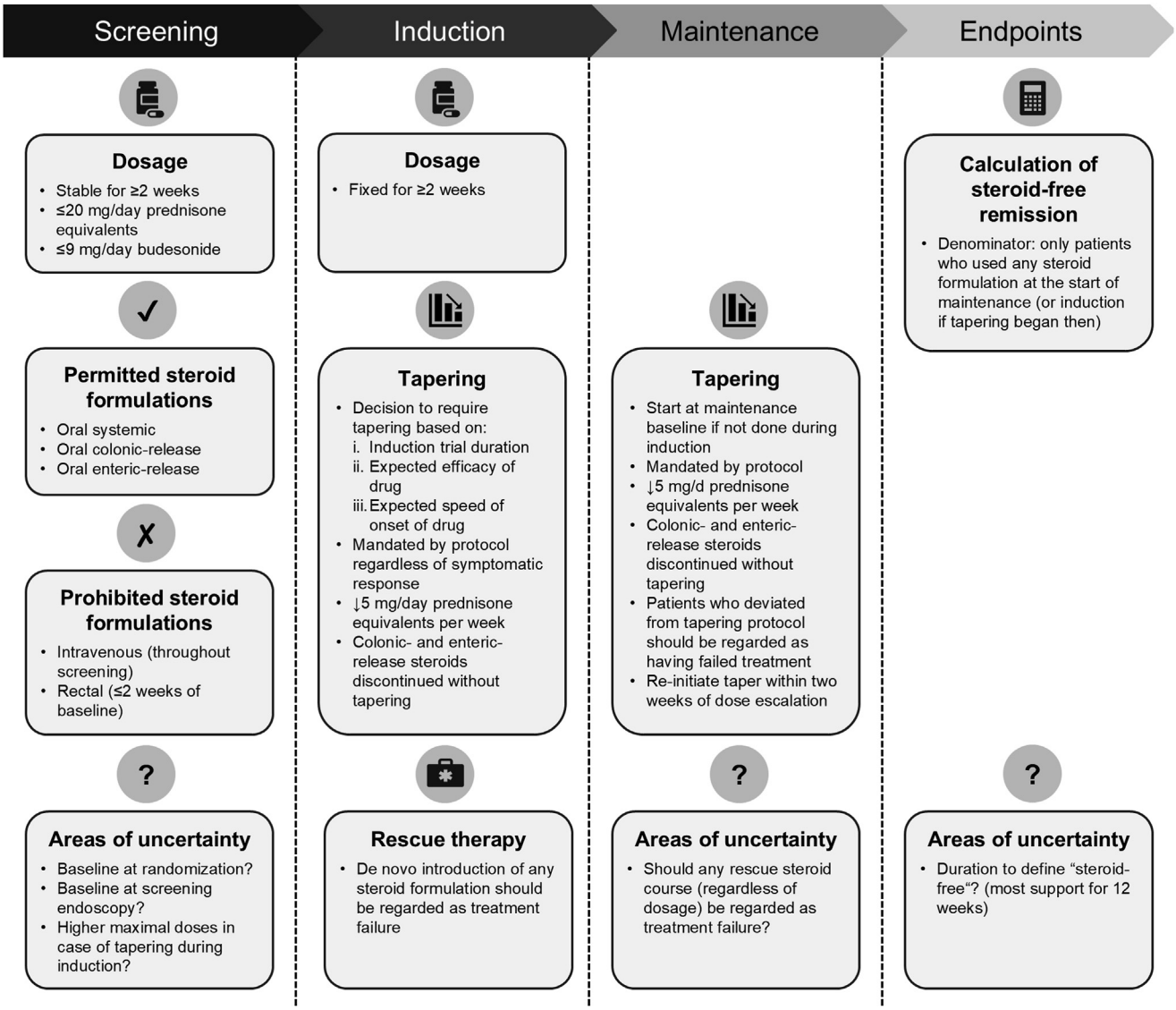

Figure 1. Summary of recommendations to be used for future trials.

the requirement of stable dosing during the screening period and, in most cases, during induction.

On the basis of these factors, the cumulative period of trial-driven corticosteroid exposure can frequently exceed 12 weeks,[3,18,19] a marker of excessive corticosteroid use associated with a range of adverse events, including increased mortality. The panelists recognized this risk and recommended a stable dosing period of 2 weeks before screening and favored beginning dosage tapering within 2 weeks of induction. Panelists discussed that a mandatory corticosteroid tapering schedule for all patients, regardless of early symptomatic response, would be best suited to highly effective agents with a rapid onset of action.[20–22] This strategy would also minimize the response to placebo[10] with the option to re-escalate the corticosteroid dosage in patients with intolerable symptoms, enabling them to enter an open-label rescue arm while being considered as having failed treatment for the purpose of the primary end point.

Corticosteroid tapering regimens vary widely between RCTs, yet relapse rates and outcomes are remarkably similar regardless of the schedule.[23–25] This observation prompted panelists to support a unified tapering protocol of 5 mg prednisone equivalents/wk to ensure operational simplicity, minimize the risk of differential tapering between treatment arms, and critically, shorten the total duration of corticosteroid exposure across trial participants. Tapering corticosteroids more gradually, rather than withdrawing them abruptly, is thought to serve 2 purposes: preventing symptomatic reactivation of IBD and allowing sufficient time for hypothalamic-pituitary-adrenal axis recovery.[26]

Despite extensive research, there is no evidence to support one tapering regimen over another to reduce the risk of developing adrenal insufficiency.[27] The current approach to systemic corticosteroids therefore appears to be justified, provided that a high index of suspicion is

maintained for symptoms of adrenal insufficiency that can often mimic worsening IBD. The panel reached consensus that enteric- and colonic-release corticosteroids do not require tapering, primarily based on observations that there is a paucity of data supporting efficacy of tapering budesonide, and historical safety data justify discontinuing budesonide formulations without significant risk of hypothalamic-pituitary-adrenal axis suppression or adrenal insufficiency.[28,29]

A point of consensus was that the beginning of tapering and its rate should both be mandated by the trial protocol and not left to the investigators' discretion. An illustrative example of the importance of protocol-defined tapering was the Efficacy and Safety Study of Vedolizumab Intravenous (IV) Compared to Adalimumab Subcutaneous (SC) in Participants With Ulcerative Colitis (VARSITY) trial, a randomized, active-controlled trial of vedolizumab vs adalimumab in moderately-to-severely active UC.[12] Clinical remission (Δ8.8%), endoscopic improvement (Δ11.9%), and most secondary outcomes were significantly more likely to be achieved with vedolizumab compared with adalimumab. Conversely, corticosteroid-free clinical remission was more likely to occur with adalimumab (Δ9.3%). This inconsistency between primary clinical remission end point and corticosteroid-free clinical remission could be explained by the absence of a specific schedule for corticosteroid tapering.[13] At the time of the trial, many clinicians regarded vedolizumab as having a more gradual onset of action,[30] which may have prompted slower corticosteroid tapering than in the adalimumab arm, although empirical evidence to support this perception is lacking.

Consensus was not reached on the duration of corticosteroid withdrawal before the final study visit for defining corticosteroid-free remission. Consistent with a prior consensus initiative,[1] 12 weeks had the highest support, although not meeting the consensus threshold. Panelists also voted that a withdrawal period of 0 to 2 weeks was not appropriate to define corticosteroid-free remission. Empirical data on this subject are limited and do not seem to support the clinical perception that a longer duration of steroid withdrawal suggests a deeper level of remission. Different definitions were explored post hoc in 3 trials of ustekinumab (2 CD and 1 UC): corticosteroid withdrawal at last study visit, $\geq$30 days before the last study visit, or $\geq$90 days before the last study visit.[31] The results were remarkably consistent regardless of the definition used.

It should be noted that all 3 trials used a protocol-mandated tapering schedule, which may have led to greater uniformity between definitions, whereby even patients receiving the maximum allowed corticosteroid doses at the beginning of the induction trial would have discontinued corticosteroids $\leq$10 weeks of starting the maintenance trial (ie, 26 weeks before the final study visit). Pending further studies on this question, the regulatory guidance remains "at least 8 to 12 weeks."[32]

During the ratification meeting discussion, panelists highlighted the need for meticulous documentation of corticosteroid use during RCTs. As noted in a prior systematic review,[4] aspects of corticosteroid management remain underreported in the final publication, despite being described in the protocol, such as the proportion of patients receiving corticosteroids as rescue medication and the proportion of patients requiring dosage re-escalation after having commenced a taper. An aspirational goal would be to report the cumulative dose of corticosteroid exposure throughout a trial to enable more informed comparison between arms within a trial as well as between trials. We hope that this consensus stimulates additional discussion and research on this topic.

Our study has several strengths. Notably, it systematically addressed important aspects of corticosteroid handling in RCTs for moderately-to-severely active CD and UC and garnered insight from a global panel of experts in IBD with broad research and clinical experience through a rigorous Delphi process. Nonetheless, we acknowledge some important limitations. First, the scope of this consensus applies to drug trials of moderate-to-severe IBD in adult patients. Considerations may be different for nondrug trials, specific phenotypes of IBD, and pediatric patients.

Second, although we provided a comprehensive list of statements to address the use of corticosteroids in RCTs, the length of surveys may have led to voter fatigue; however, steps were taken to mitigate this by allowing panelists to complete surveys in multiple sittings and by organizing statements in sections. Panelist fatigue could conceivably have led to incomplete responses and skewed consensus on some of the more technical details, such as duration and dosing.

Third, we recognize that the use of corticosteroids is directly impactful for patients and that the patient perspective is critical for dictating many of these considerations. Patients reviewed the statements post hoc and provided additional input from the patient perspective.

Finally, no input on the work was sought from regulatory authorities who have a key impact on clinical trial design.

Conclusion

We have developed the first internationally guided set of recommendations for corticosteroid management in RCTs of adult patients with IBD treated with pharmacologic therapies. These recommendations will serve to optimize RCT design and potentially facilitate appropriate, acceptable, and uniform corticosteroid handling in RCTs that is more consistent with clinical care.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2025.05.015.

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Conflicts of interest
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Data Availability
Data, analytic methods, and study materials will be made available to other researchers upon reasonable written request.