Alternate Endpoints and Clinical Outcome Assessments in Pediatric Ulcerative Colitis Registration Trials

*Haihao Sun, †Jessica J. Lee, ‡Elektra J. Papadopoulos, *Catherine S. Lee, *Robert M. Nelson, §Hari C. Sachs, *William J. Rodriguez, and †Andrew E. Mulberg

ABSTRACT

Objectives: Presently, there is no consensus on endpoint measures to assess clinical outcomes for pediatric ulcerative colitis (UC). This study reviewed the endpoints used in the registration trials of approved drugs for pediatric UC.

Methods: The primary efficacy endpoints of all registration trials completed from 1950 to 2008 that led to Food and Drug Administration approval for indications in pediatric and adult UC were reviewed.

Results: Colazal and Remicade have been approved for pediatric UC indication, and clinical response was used as a primary endpoint in these registration trials. The clinical response in the adult Colazal trials was defined as a reduction of rectal bleeding and improvement in at least one of the other assessed symptoms (stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment) assessed by the Sutherland UC Activity Index. The pediatric Colazal trial defined clinical response using the Modified Sutherland UC Activity Index, which excluded abdominal pain and functional assessment. Both adult and pediatric Remicade trials used clinical response defined by the Mayo score as the primary endpoint. The Pediatric Ulcerative Colitis Activity Index was used to measure various secondary endpoints in the pediatric Remicade trial.

Conclusions: Pediatric-specific endpoints were used, but outcome measures and definition of clinical response were not consistent in pediatric UC trials. Consensus on the definition of successful treatment outcome (clinical response and/or remission) and collaboration in the development of well-defined and reliable measures of signs and symptoms for use in conjunction with endoscopic parameters of mucosal healing will facilitate pediatric drug development.

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From the *Office of Pediatric Therapeutics, Office of the Commissioner, the †Division of Gastroenterology and Inborn Errors Products, the ‡Study Endpoint and Labeling Development (SEALD), and the §Pediatrics and Maternal Health Staff, Office of New Drug, Center for Drug Research and Evaluation, Food and Drug Administration, Silver Spring, MD.

Address correspondence and reprint requests to Andrew E. Mulberg, MD, FAAP, Division of Gastroenterology and Inborn Errors Products, Office of New Drug/Center for Drug Research and Evaluation/Food and Drug Administration, Food and Drug Administration, 10903 New Hampshire Avenue, Building 22, Room 5120, Silver Spring, MD 20993 (e-mail: Andrew.Mulberg@fda.hhs.gov).

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There is a need to develop effective therapies to treat pediatric ulcerative colitis (UC). The Food and Drug Administration (FDA)–approved medical treatment of UC in the pediatric population is limited to Azulfidine (sulfasalazine), Colazal (balsalazide disodium), and Remicade (infliximab). One of the challenges in conducting pediatric clinical trials may be the lack of appropriate pediatric endpoints. Pediatric endpoints are defined as primary (or secondary) outcome measures, specifically designed for the pediatric population, used to assess the effect of study treatment. These endpoints may be different from those used in adult clinical trials and thus are referred to as alternate endpoints. Similar to adult UC, there does not appear to be consensus on pediatric endpoint measures that assess the treatment outcome in pediatric UC trials. For example, the Simple Clinical Colitis Activity Index, the Mayo score, and Pediatric UC Activity Index (PUCAI) have been used in various trials to assess disease activities and treatment outcomes (1–3). A systematic review of alternate endpoints used in pediatric UC registration trials has not been conducted.

Harmonization of pediatric alternate endpoints and outcome measures is needed to facilitate future pediatric UC trials and global drug development. Toward these efforts, the overall objective of this study is to review the alternate endpoints that have been used in pediatric UC registration trials. Specifically, the objectives are to review the primary endpoints and their assessment instruments in the registration trials of the approved therapies for pediatric UC; evaluate the use of the alternate endpoints and outcome measures in the pediatric UC trials of the approved therapies; and examine the effect of different endpoints and remission definitions on the outcome of the clinical trial.

UC is associated with a complex of signs and symptoms consisting of abdominal pain, diarrhea, blood in stool, and other clinical signs and symptoms. Assessments of signs and symptoms include patient-reported outcome (PRO) and observer-reported outcome (ObsRO) measurements. The principles of measuring PRO concepts in children and adolescents are described in the ''Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims'' (4). In general, PRO instruments for children and adolescents should include consideration of age-appropriate vocabulary to ensure comprehension of language and health concepts being measured, and duration of recall. Proxy-reported outcome measures (ie, reports by someone who is not the patient responding as if that person were the patient) are discouraged for use in registration trials as suggested by the FDA PRO guideline (4). For patients who cannot respond on their own (eg, infants), observer reports,

including only events or behaviors that are directly observable, are recommended. For example, observers cannot validly report an infant's pain intensity, which is not observable and known only to the patient, but can report infant behavior thought to be caused by pain.

There is a lack of consensus on the definition of clinical response and remission in pediatric UC trials and whether this is best measured through the use of a multicomponent measure that comprises clinician-reported outcome measures, PRO measures, and biomarkers versus the use of these parameters as individual endpoints or composite endpoints (1).

It is worthy to note that Crohn disease (CD) is another entity of inflammatory bowel disease. Unlike UC, CD is a transmural process that can result in mucosal inflammation and ulceration, stricturing, fistula development, and abscess formation (5). Hence, different disease activity indices, such as Pediatric CD Activity Index (PCDAI), are used in pediatric CD trials to assess the study outcomes. Similar to UC, efficacy endpoints and outcome measures play an important role in pediatric CD trials and drug development. The challenges associated with efficacy endpoints and outcome measures in pediatric CD registration trials are reported separately.

METHODS

Review of Trial Data Submitted to the FDA

The registration trial data submitted from 1950 to 2008 were retrieved from FDA's Document Archiving, Reporting, and Regulatory Tracking System or the document room (if the electronic copies were not available). The primary efficacy endpoints of all completed trials (Remicade and Colazal) that led to FDA approval for indications in pediatric UC and adult UC were reviewed. The primary efficacy endpoints and clinical outcome assessments that were used to measure these endpoints in pediatric and adult UC trials were compared for each product as well as across products. Descriptive tables were used to present the data from each trial and to compare the differences in study endpoints and activity indices between pediatric and adult trials. Then, the presence of alternate endpoints and the adequacy of clinical outcome assessments to measure these endpoints were assessed. To explore whether different endpoints and remission definitions would have an effect on the trial outcome, the remission definition of the Mayo score and PUCAI used in the pediatric Remicade registration trial was examined, and the remission rates resulting from the Mayo score and PUCAI measurement were compared.

Assessment of the Clinical Outcome Assessment Tools Used in Pediatric UC

The content validity of each clinical outcome assessment tool was assessed based on the principles described in ''Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims'' (4). In general, clinical outcome assessment tools should be reliable, valid, and able to detect clinically meaningful change in the concept of interest. The FDA PRO guidance defines content validity as the extent to which the instrument measures the concept of interest (4). The concept is, as defined by the FDA, the thing being directly measured by an assessment. Content validity is supported by evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and context of use. Content validity may be specific to the population, condition, and treatment to be studied. For PRO, ObsRO, and clinician-reported outcome (ClinRO) instruments, items, domains, and general scores should reflect what is important to patients. The application of content validity applies equally to the development of ClinROs as well as to PROs and is applied to the therapeutic areas, which choose to develop this type of clinical outcome assessment tool. Documentation of patient input in item generation as well as evaluation of patient understanding through cognitive interviewing can contribute to evidence of content validity (4,6,7). Without adequate documentation of patient input, a PRO instrument's content validity is likely to be questioned. FDA evaluates the content validity to determine whether the instrument measures the concept that it was intended to measure (4). In the absence of evidence of content validity, other measurement properties cannot be interpreted.

Review of Published Literature

The electronic database PubMed/MEDLINE was searched using phrases such as ''adult ulcerative colitis/AND (disease activity indices or instrument)'' and ''pediatric ulcerative colitis/AND (disease activity indices or instrument).'' No language and time restrictions were applied during the search. The last search was conducted on February 15, 2013. Only randomized controlled clinical trials and review articles addressing study endpoints, outcome measurements, and disease activity indices were considered for the review. The purpose of the literature review was to understand the present state of the efficacy endpoints used in adult and pediatric UC trials. The evidence found in the literature review was used as a reference to confirm or challenge what was found in the review of the registration trials that led to FDA approval for indications in pediatric UC and adult UC.

RESULTS

Based on the pediatric trial data submitted to the FDA from 1950 to 2008, we identified 3 different disease activity indices that were used in pediatric UC trials for 3 approved products. Modified Sutherland UC Activity Index (MUCAI) was used in the Colazal pediatric trial (2006), and the Mayo score and PUCAI were used in the Remicade pediatric trial (2011). Azulfidine was initially approved for the UC indication in 1950 and fell into the domain of the Drug Efficacy Study Implementation Amendment that applies to drugs approved by FDA before 1962, when Congress determined that efficacy of drugs had to be established before marketing approval. The approval of Azulfidine for the pediatric UC indication was granted in 2009, based on a full extrapolation of efficacy from adult trials; therefore, no pediatric trial was conducted.

Alternate Endpoints Used in the Pediatric UC Trials

As shown in Table 1, clinical response was the primary efficacy endpoint in both adult and pediatric Colazal trials. The primary efficacy endpoint in the adult Colazal trials was reduction of rectal bleeding and improvement in at least one of the other assessed symptoms (stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment), which were measured by the Sutherland UC Activity Index. Reduction of rectal bleeding and improvement of clinical symptoms was defined as a 1-point decrease for each, which indicated that the clinical response in this adult trial was defined as an at least 2-point decrease in the Sutherland UC Activity Index. The primary efficacy endpoint of the pediatric Colazal trial was the proportion of patients with clinical improvement assessed by the MUCAI, which includes measurements of stool frequency, rectal bleeding, physician's global assessment, and endoscopy (8). This

TABLE 1. Primary endpoints and alternate endpoints used in pediatric UC trials

	Primary endpoints and their definitions	
	Pediatric trials	Adult trials
Colazal	Clinical response measured by the MUCAI at week 8; clinical response was defined as a proportion of subjects with clinical improvement, defined as a reduction from baseline to week 8 in the MUCAI score by at least 3 points	Clinical response measured by the Sutherland UC Activity Index at week 8; clinical response was defined as reduction in rectal bleeding and improvement in at least one of the other assessed symptoms (stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment). Outcome assessment for rectal bleeding at each interim period (week 2, 4, and 8) encompassed a 4-day period (96 hours).
Remicade	Clinical response measured by the Mayo score at week 8; clinical response was defined as a decrease from the baseline Mayo score by $\geq$30% and $\geq$3 points, with a decrease in the rectal bleeding subscore of $\geq$1 or achievement of rectal bleeding subscore of 0 or 1	Clinical response measured by the Mayo score at week 8; clinical response was defined as a decrease from the baseline Mayo score by $\geq$30% and $\geq$3 points, with a decrease in the rectal bleeding subscore of $\geq$1 or achievement of rectal bleeding subscore of 0 or 1

MUCAI = Modified Ulcerative Colitis Activity index.

indicated that the clinical improvement in the pediatric UC trial was defined as an at least 4-point decrease in the MUCAI. Compared with the Sutherland UC Activity Index, MUCAI does not have the components of abdominal pain and patient functional assessment (8). In addition, both adult and pediatric Remicade trials used the Mayo score to assess the primary efficacy endpoint. The primary endpoint, clinical response, was defined as a decrease from the baseline Mayo score by $\geq$30% and $\geq$3 points, with a decrease in the rectal bleeding subscore of $\geq$1 or achievement of rectal bleeding subscore of 0 or 1 in both adult and pediatric Remicade trials (9). The components of the Mayo score are discussed in the next section, as well as shown in Table 2 (9–11). The PUCAI was used to measure various secondary endpoints in the pediatric Remicade trials. The components of the PUCAI are also discussed in the next section and shown in Table 2.

Disease Activity Indices Used in the Pediatric UC Trials

Table 2 compares the components of disease activity indices and definitions of the grading systems used in pediatric UC trials. Although both MUCAI and Mayo Score include the endoscopic mucosal appearance component, the grading score is defined differently. The PUCAI does not include mucosal assessment and is intended to be a noninvasive measure of disease activity.

As shown in Table 3, rectal bleeding, diarrhea, lower abdominal cramps, fecal urgency, and sigmoidoscopic appearance are considered the key signs and symptoms in the patients with UC (5). Each of the 3 existing disease activity indices used in pediatric UC trials measures most, but not all, of the key signs and symptoms of pediatric UC. For example, although all 3 instruments assess rectal bleeding and diarrhea, no instrument measures urgency and incontinence, which are very important to patients (5,12). Abdominal pain, an important symptom to young children (13), is captured only in PUCAI.

Assessment of the Disease Activity Indices Used in the Pediatric UC Trials

MUCAI is a modification of the Sutherland UC Disease Activity index, and thus it is similar but not identical to the primary efficacy endpoint used in the adult trial. The MUCAI used concrete signs (rather than symptoms) that the parent or the child can observe. For example, rather than using the term ''diarrhea,'' which is often ill-defined by patients, the MUCAI uses ''number of stools per day,'' which is an easily quantifiable variable. The other clinical sign assessed by the MUCAI is rectal bleeding, which can be easily identified by a patient or parent. In addition, the MUCAI includes mucosal appearance and a global rating of disease activity, which is assessed by the physician.

The Mayo score also consists of 4 categories (rectal bleeding, stool frequency, physician assessment, and endoscopic appearance) that are rated from 0 to 3 and give rise to a total score ranging from 0 to 12 (Table 2). It is the most commonly used instrument in placebo-controlled clinical trials for UC (1,10,14–17). Unlike the MUCAI, the Mayo stool frequency subscore is not an absolute stool count number, but is scored relative to ''normal'' for that subject, which may introduce interobserver variation. Additionally, the percentage of blood content–estimated patients may also introduce interobserver variation. Thus, a PRO component that assesses episodes of rectal bleeding not associated with stool may need to be considered. Further refinement of this endpoint may need to be considered.

The PUCAI was developed as a noninvasive disease activity index for pediatric UC and is reported to be correlated with colonoscopy ($r = 0.77$) (13). It is a physician-administered measure that focuses on 6 key signs and symptoms of UC: abdominal pain, rectal bleeding, stool consistency, number of stools per 24 hours, nocturnal stools (any event causing awakening), and activity level, which gives a maximum score of 85 (Table 2). The item selection of the PUCAI was performed by a group of 36 experts in pediatric inflammatory disease. The item weighting was performed by regression modeling using a prospective cohort of 157 pediatric patients with UC with a physician global assessment of disease activity as the anchor. A physician-based rather than a patient-based approach was used in the PUCAI during the instrument development process because the developers believe that disease activity is best judged by experienced physicians (13).

Because physicians obtain and interpret the information, the PUCAI is a proxy report, not a PRO or ObsRO. Additionally, the source of the information, that is, whether it is the child or caregiver, is unclear and can be variable. The extent to which the physician completing the assessment includes his or her own interpretation is unclear. The lack of standardization in measurement introduces variability and results in concepts of measurement (disease activity, response, and remission) being variably defined. Furthermore,

TABLE 2. Disease activity indices used in the pediatric UC trials (9–11)

Instruments	MUCAI	Mayo score	PUCAI
Components	Stool frequency/day (score)	Stool frequency/day (score)	Abdominal pain
	0: ≤ 3 stools/day	0: Normal number of stools for this patient	0: No pain
	1: 4–5 stools/day	1: 1–2 stools more than normal	5: Pain can be ignored
	2: 6–7 stools/day	2: 3–4 stools more than normal	10: Pain cannot be ignored
	3: ≥ 8 stools/day	3: 5 or more stools more than normal	Rectal bleeding
	Rectal bleeding or blood in stool (score)	Rectal bleeding or blood in stool (score)	0: None
	0: None	0: No blood seen	10: Small amount, more than half stools
	1: Streaks of blood	1: Streaks of blood less than half the time	20: Small amount with most stools
	2: Obvious blood	2: Obvious blood most of the time	30: Large amount (>50% of the stool content)
	3: Mostly blood	3: Blood alone passed	Stool consistency of most stools
	Physician's rating of disease activity	Physician's rating of disease activity	0: Formed
	0: Normal	0: Normal	5: Partially formed
	1: Mild	1: Mild	10: Completely unformed
	2: Moderate	2: Moderate	Number of stools/24 hours
	3: Severe	3: Severe	0: 0–2
	Mucosal appearance	Mucosal appearance	5: 3–5
	0: Intact mucosal with preserved or distorted vessels	0: Normal or inactive disease	10: 6–8
	1: Edematous mucosal with granularity and mild friability without ulceration	1: Mild disease (erythema, diseased vascular pattern, mild friability)	15: >8
	2: Pinpoint ulceration and moderate friability	2: Moderate disease (marked erythema, absent vascular pattern, friability, erosion)	Nocturnal bowel movement (any diarrhea episode causing wakening)
	3: Gross ulceration and spontaneous hemorrhage	3: Severe disease (spontaneous bleeding, ulceration)	0: No
			10: Yes
			Activity level
			0: No limitation of activity
			5: Occasional limitation of activity
			10: Severe restricted activity
Total score	12	12	85

MUCAI = Modified Ulcerative Colitis Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index.

unobservable concepts such as pain can only be assessed via direct report; if direct report is not feasible, such concepts must be assessed indirectly based on observable signs. The ability of the individual to ignore pain (PUCAI abdominal pain item) may be related to various other factors unrelated to the disease. In addition, the PUCAI lacks an adequate age-appropriate interviewer script and response rating criteria for the physician interviewer. Published work by Lee et al in 2011 demonstrated strong agreement between PUCAI scores obtained directly from patients and those completed by physicians. Additionally, a comparison study of noninvasive disease activity indices conducted in 86 adults with UC has demonstrated that PUCAI correlated with colonoscopic score better

TABLE 3. Comparison of key clinical features of UC captured in pediatric UC disease activity indices

Key clinical features of UC	MUCAI	Mayo score	PUCAI
Rectal bleeding	Captured	Captured	Captured
Diarrhea	Captured	Captured	Emphasized
Lower abdominal cramps	Not captured	Not captured	Captured
Fecal urgency	Not captured	Not captured	Not captured
Sigmoidoscopy*	Captured	Captured	Not captured

Captured = collected component of instrument; emphasized = collected component multiple times; MUCAI = Modified Ulcerative Colitis Activity Index; not captured = not collected component of instrument; PUCAI = Pediatric Ulcerative Colitis Activity Index.
* Necessary to confirm diagnosis and to evaluate mucosal appearance.

TABLE 4. Impact of remission definition on clinical outcome of the Remicade pediatric UC Trial

Study/drug	Instrument	Remission definition	Remission score	Remission rate
Remicade	Mayo score	Clinical remission defined by Mayo score: a Mayo score ≤2 with no individual subscore >1 at week 8	≤2	40% (24/60)
Remicade	PUCAI	Clinical remission was defined as a PUCAI score <10 at week 8	<10	33% (17/51)

PUCAI = Pediatric Ulcerative Colitis Activity Index.

than partial Mayo score (0.74 vs 0.69, respectively) (11). Whether a patient-based PUCAI could complement existing instruments in both clinical and research settings remains to be confirmed in multiple clinical trials or in a registration setting (18). Therefore, there are features of PUCAI that, if addressed, could improve its ability to serve as an efficacy endpoint in a clinical trial to evaluate a product for the treatment of UC in the pediatric population.

Impact of Different Clinical Remission Definitions on the Clinical Outcome

In the pediatric Remicade trial, the baseline disease activity was measured by both PUCAI and Mayo score. All enrolled patients received Remicade 5 mg/kg intravenous infusion at weeks 0, 2, and 6. At week 8, these patients were evaluated for clinical remission rate measured by both PUCAI and Mayo score. Clinical remission was defined by Mayo score of ≤2 with no individual subscore >1, whereas it was defined by PUCAI as a score <10. As shown in Table 4, 24 of 60 patients (40%) were in clinical remission when assessed by Mayo score, whereas 17 of 51 patients (33%) were in clinical remission when assessed by PUCAI. This observation indicates that different endpoint measures with different definitions of the treatment outcome may affect the clinical trial outcome.

DISCUSSION

Alternate endpoints were used in the Colazal pediatric trial. Alternate endpoints were also used as a secondary endpoint, but not as a primary endpoint in the Remicade pediatric trial. There is lack of consistency in the definition of primary efficacy endpoints assessing treatment outcome in adult and pediatric UC registration trials. The reason for the inconsistency may be historical precedence, evolving science, and availability of clinical outcome measures. There is currently no consensus on endpoints and clinical outcome measures to assess the clinical outcome in pediatric UC. In addition, different clinical remission definitions may affect the clinical or trial outcomes. Standardized outcome concepts and remission definitions for use as trial endpoints to define treatment benefit are needed to facilitate the pediatric UC drug development.

Using qualitative research in patients and caregivers, an instrument should have adequate content validity (evidence that the score represents the concept of interest and that the item response options, and item weights are appropriate and interpretable) for the target population. In establishing content validity, it is important to identify the lower age limit at which children can understand the questions and provide reliable and valid responses. Multiple versions specific to appropriate age ranges within the targeted patient population (not just a single form) will need to be considered. More important, observer (including caregiver) reports should only include those events or behaviors that can be observed. Taking the example of pain, observers cannot validly rate a child's pain intensity but can report on behaviors and observable signs thought to be caused by pain.

Instrument items should be specific and conceptually simple, representing the concepts that define treatment benefit in the targeted subpopulations. Diagnostic tools do not necessarily capture concepts most important for measuring treatment benefit. Ratings of pain on the basis of ''can be ignored'' or ''cannot be ignored'' are discouraged because such responses are affected by many other variables other than the intensity of the symptom. Therefore, a PRO that includes a simple rating of abdominal pain intensity (eg, worst pain intensity in past 24 hours) should be considered. Similarly, it is not feasible for patients to estimate the percentage of stool content that consists of blood; thus, a PRO instrument that assesses concepts, such as number of bloody stools and episodes of rectal bleeding not associated with stool, should be considered.

The collaboration of interested parties, including international regulatory bodies, pharmaceutical industry, academia, and patient groups, in the development of adequate outcome measures in pediatric UC is highly encouraged. To facilitate the development of publicly available scientific tools to address unmet needs such as this, the FDA has initiated a drug development tool qualification program that provides a framework for the development and regulatory acceptance of scientific tools, including clinical outcome assessments, intended for well-specified clinical trial contexts of use (19).

In summary, no existing outcome measures are adequate to measure pediatric UC treatment outcome. No preferred primary efficacy endpoints were identified. To optimize the information for labeling and the correct use of the drug, clinical trials designed to evaluate the efficacy of medical therapies require clearly defined outcome endpoints and a well-recognized definition of disease remission. Consensus on definition of successful treatment outcome (disease response and/or remission) would facilitate pediatric drug development. A well-designed, reliable, and globally recognized outcome measure that measures signs and symptoms in children with UC is needed for expediting pediatric drug development. An age-appropriate set of tools to be completed by an observer or the child, as appropriate, should be based on a firm understanding of disease definition according to clinically meaningful subgroups, and other aspects of the context of use, to ensure content validity. Endoscopic mucosal and histological examination may need to be considered as 1 outcome measurement as the community is actively evaluating the critical role of mucosal healing, which should encompass both gross and microscopic evidence of disease activity. Whether these concepts can best be assessed for by a combination of PRO, ClinRO, and biomarkers, or through the use of individually scored signs and symptoms, remains a topic for further discussion.

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