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Development of Celiac Disease Therapeutics: The Sixth Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics Workshop

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The Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI Workshop, held on July 22, 2021, provided a forum for patients and representatives from academia, industry, patient advocacy groups and FDA to discuss drug development for celiac disease (CeD). The workshop focused on the approach to histologic assessments in clinical trials, considerations for pediatric drug development, and use of a gluten challenge (GC) in clinical trials. Given that no histologic scoring system is widely accepted for use in clinical trials at this time, early phase clinical trials should ideally explore a variety of histologic scales and assess the histologic findings of celiac disease as individual measures to inform future trials. When planning pediatric drug development in CeD, appropriate use of extrapolation of efficacy data from adequate, well-controlled studies in adults could facilitate timely access to safe and effective therapies for pediatric patients. Identification of a fit-for-purpose pediatric clinical outcome assessment could further advance pediatric drug development. Histologic responses to the GC depend on exposure dose and duration; short exposures do not appear to cause long-term consequences. However, the GC should be incorporated into clinical trials in a thoughtful manner to generate interpretable results and ensure patient safety. Ongoing collaboration between all stakeholders will facilitate the development of safe and effective therapeutics for CeD.

Introduction

Celiac disease (CeD) is a chronic disorder caused by an immune reaction to ingested gluten that primarily affects the small intestine, and produces a variety of gastrointestinal and extraintestinal symptoms. A gluten-free diet (GFD) is currently the only treatment. Although strict compliance with a GFD is effective for many patients, maintaining the diet and avoiding inadvertent gluten exposure can be challenging. Therefore, an unmet need exists for pharmacologic therapies for CeD.

The Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI) workshop on CeD was held July 22, 2021, sponsored by the Food and Drug Administration (FDA) in collaboration with the American College of Gastroenterology, the American Gastroenterological Association, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. The workshop was attended by stakeholders from academia, clinical practice, industry, FDA, patients, and patient advocacy groups. Herein are summarized the topics covered in the workshop. Details regarding the presentations can be found at <http://www.fda.gov/drugs/news-events-human-drugs/gastroenterology-regulatory-endpoints-and-advancement-therapeutics-vi-great-vi-workshop-celiac>.

Session 1: Histologic Assessment in Evaluation of the Underlying Disease and Treatment Benefit in Celiac Disease

Dr. Benjamin Lebwohl reviewed approaches to monitoring the underlying disease using histologic assessment in clinical practice for adults. Clinicians often rely on a combination of factors when assessing response to a GFD, including improvement in clinical symptoms, serologies, and histology. Symptoms and serology are not reliable predictors of persistent villous atrophy in CeD^{1,2}. Although the role of follow-up biopsy in the management of CeD in clinical practice remains uncertain, there appear to be untoward consequences of persistent villous atrophy. A follow-up biopsy may help determine the response to a GFD, and whether ongoing symptoms are due to gluten exposure or other factors (e.g., functional gastrointestinal disorders), because persistent villous atrophy suggests ongoing gluten

exposure. The American College of Gastroenterology clinical guidelines state that obtaining a follow-up biopsy is reasonable in adults after 2 years of starting a GFD to assess healing³. Age appears to be an important predictor of intestinal healing and children are more likely to heal, and heal more rapidly, than adults⁴. Adults with CeD may take a year or longer for the underlying inflammation to resolve on a GFD. Patients are often characterized in clinical practice as healed or not healed; however, there is a continuum of response that could be evaluated using the distinguishing histologic features of CeD.

Dr. Jocelyn Silvester shared several considerations for using histologic assessments in clinical practice to monitor pediatric patients with CeD. Assessing mucosal recovery is not routinely performed in pediatric patients on a GFD; however, a follow-up biopsy may be useful for patients with new or ongoing symptoms, persistently elevated serology, or comorbidities assessed by routine follow-up biopsies (e.g., eosinophilic esophagitis)⁵. Defining histologic improvement in clinical trials can be challenging because pediatric patients do not routinely undergo repeat biopsies, and the reporting of histology in clinical practice tends to be less rigorous than in clinical trials.

Dr. Marie Robert provided a pathologist's perspective on histologic assessment in CeD. Several different classification systems (e.g., Marsh-Oberhuber, Corazza and Vilanaci, Ensari) are used to assess the underlying disease state in CeD; however, no system is widely accepted for use in clinical trials at this time. Ideally, clinical trials should collect histologic data in a variety of ways to maximize the scientific gain. Because intraepithelial lymphocyte (IEL) recovery may lag behind normalization of villi, villous architecture could be dissociated from IEL counts. Standardizing the approach to histologic scoring and tissue handling, including biopsy location and number, and fixation and orientation of samples, is important for clinical trials. Using centralized laboratories may reduce variability.

Panelists discussed that performing follow-up biopsies to evaluate histologic improvement in patients with active disease may be reasonable after 6 to 12 months of treatment in a trial (and in another 1 to 2 years to assess for more-complete healing); however, evaluating histologic changes after a shorter time may be practical after a gluten challenge. There was consensus on the importance of relying on well-

oriented samples and a standardized process for histologic scoring. The clinicians on the panel appreciated the importance of therapies that can improve both patient symptoms and the underlying intestinal damage. Additionally, patients may be willing to undergo endoscopies in clinical trials if they understand how the data may inform the results of the trial and advance the science; education is part of the role of trial investigators.

Session 2: Pediatric Celiac Disease

FDA described that appropriate use of extrapolation of efficacy data to a pediatric population from adequate, well-controlled studies in adults can promote timely access to safe and effective therapies for pediatric patients. The ability to extrapolate is based on the quality, quantity, and relevance of the adult efficacy data to the target pediatric population, and whether the available data support the assumptions of similarities in the disease and treatment response between the two populations. The degree of confidence in the assumptions dictates what additional pediatric data are needed. Planning for pediatric trials early helps to ensure that certain design elements are incorporated into the adult program to facilitate extrapolation of efficacy for the pediatric program.

Dr. Maureen Leonard presented the clinical manifestations, natural history, and unmet needs of pediatric CeD. Pediatric-specific manifestations of CeD include short stature, delayed puberty, dental enamel defects, and behavioral changes^{6,7}. Initiation of a GFD is the treatment irrespective of the presentation at diagnosis, disease duration, symptoms, or age. There are distinct challenges as patients progress through childhood with less parental control of their diet, necessitating alternative treatment options.

FDA shared the regulatory perspective on assessing clinical benefit in pediatric trials. Clinical benefit is defined as a favorable effect of a treatment on a meaningful aspect of how a patient feels, functions, or survives. Clinical outcome assessments (COAs), such as patient-reported outcomes (PROs), are used to assess how a patient feels or functions^{8,9}. COAs should be well-defined and reliable in their specific context of use (“fit-for-purpose”) to support regulatory decision-making. Evidence should be provided to

support content validity, measurement properties, and interpretation of meaningful change. Interpreting meaningful changes in COA scores involves using quantitative anchor-based scoring methods and qualitative evidence (e.g., results of exit interviews with patients or caregivers).

A patient diagnosed with CeD at 11 years of age provided his perspective on living with CeD. He experienced abdominal pain, nausea, vomiting, and diarrhea. Fortunately, strict adherence to a GFD relieved his symptoms; however, the potential for inadvertent gluten exposure hampers social activities, including traveling and eating outside of the home. The possibility of new therapies to complement a GFD brings hope.

Panelists generally considered symptoms between the adult and pediatric CeD populations to be similar, but not identical, and discussed that since CeD in the two populations has a common pathogenesis, the potential drug targets could be the same. Advances toward identifying a fit-for-purpose COA for pediatric CeD could move pediatric drug development forward.

Session 3: Gluten Challenge in Clinical Trials

Dr. Joseph Murray provided an overview on using a prescribed gluten challenge in clinical practice, primarily as part of the initial diagnosis in patients on a GFD, and contraindications to performing a gluten challenge (e.g., history of anaphylaxis to wheat or gluten, severe neurologic manifestations of CeD)^{3,10}. The histologic changes due to gluten exposure likely depend on the dose and duration of exposure. In clinical practice, the follow-up of patients with CeD is based on general expectations that symptoms tend to resolve in 1 to 3 months, and serology levels fall substantially in about 6 months and are often negative at 1 year^{3,11}. Repeat biopsy after 1 to 2 years may be performed in adults, but is not mandatory in all patients doing well on a GFD without an increased risk of complications.

Dr. Jason Tye-Din summarized the dose and duration of gluten exposure that elicits clinical signs and symptoms and changes in histology based on several published studies of varying design on the effects of gluten challenge in CeD^{10, 12-16}. Histologic changes in villous-height-to-crypt-depth ratio appear to occur

on a continuum from healing to injury. Understanding the baseline disease activity is important, including how the baseline status will be factored into the trial design. Additionally, symptoms are not always caused by gluten (e.g., functional gastrointestinal disorders occur frequently in patients with CeD and symptoms can be triggered by non-gluten components of food)¹⁷. Moreover, symptoms that patients expect to have from gluten exposure may not be the symptoms that they experience during a gluten challenge. Therefore, the PRO measures should be designed to capture the symptoms that are driven by gluten exposure. A standardized approach to the gluten challenge is needed to minimize heterogeneity and yield interpretable results to advance drug development.

Dr. Daniel Leffler provided the industry perspective on the role of gluten challenges in clinical trials. While gluten exposure causes symptoms, elevations in celiac serologies, and histologic changes, a short exposure should not increase the risk of long-term complications, or cause permanent intestinal damage or ongoing symptoms after the trial is complete. Gluten challenges are used in proof-of-concept and dose-finding studies assessing therapeutic protection against gluten-induced disease activation. Simulated inadvertent gluten exposure can be used to reduce trial effects, wherein some patients may adhere more strictly to a GFD during a trial. Operational challenges for studies utilizing gluten include i) slower enrollment due to concerns with gluten exposure; ii) potential for missed gluten doses that may confound the results; iii) dropouts due to gluten-related symptoms; and iv) lack of standardization of gluten amount and form. When and how to use gluten in trials warrants careful consideration.

During the discussion, panelists discussed that introducing gluten, whether in the context of a formal challenge or as intermittent exposure, could increase the likelihood of demonstrating efficacy in certain circumstances. Patient hesitancy to enroll in clinical trials with gluten challenges could be addressed through improved education on the purpose of the gluten challenge, and benefits and risks of trial participation. Panelists also highlighted the importance of differentiating gluten-driven symptoms from those that arise from other causes. It can be challenging to differentiate symptoms that are gluten-driven

from those due to ongoing enteropathy in patients with CeD, as patients with total villous atrophy may experience symptoms from other foods.

Discussion

There remains a need for pharmacologic therapies to treat CeD. Prospective collection of data on various outcome measures that assess different histologic features of CeD in clinical trials may advance the field.

Pediatric patients with CeD generally have similar symptoms to adult patients; however, intestinal inflammation may improve earlier and possibly more completely than adults. There are other unique pediatric considerations that should be factored into designing clinical trials. Although extrapolation of efficacy from adult data may be possible, the extent to which pediatric trials can rely on adult efficacy data warrants further discussion. When necessary, a gluten challenge should be incorporated to produce interpretable results that cannot be obtained by other means, and designed to ensure patient safety.

Ongoing collaboration between academia, industry, patients, and regulatory agencies is critical to move the field forward.

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