

AGA CLINICAL PRACTICE UPDATE: MEETING SUMMARY

Development of Celiac Disease Therapeutics: Report of the Third Gastroenterology Regulatory Endpoints and Advancement of Therapeutics Workshop



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Celiac disease has been an outlier among intestinal diseases. Although not as prevalent as irritable bowel syndrome, it is significantly more common than inflammatory bowel disease.¹ Although patients are rarely hospitalized or undergo surgery due to celiac disease, attributable mortality is increased and burden of treatment, defined as the degree of difficulty in following treatment, is higher than other common luminal diseases.²

Despite the prevalence, morbidity, and treatment burden, there is significant unmet medical need for pharmacologic interventions beyond a gluten-free diet (GFD). At the time of the workshop, fewer than a dozen randomized controlled therapeutic trials had been published. Major historical obstacles to drug development include misperceptions that celiac disease is rare and mild, and that the GFD is a near-optimal therapy. In addition, there has been no precedent product approval for celiac disease that defines a guiding regulatory pathway for product developers.

On March 31, 2015, the third Gastroenterology Regulatory Endpoints and Advancement of Therapeutics (GREAT 3) workshop was held, which was sponsored by the Food and Drug Administration (FDA) Center for Drug Evaluation and Research, with co-sponsorship by the American Gastroenterological Association; the American College of Gastroenterology; the American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; and the North American Society for the Study of Celiac Disease. The meeting covered defining target populations for pharmacologic therapies, and defining and measuring clinical benefit in celiac disease trials to support marketing approval.

Session 1: Defining Target Patient Population(s) for Pharmacological Therapies

The first session of the workshop was dedicated to identifying and classifying patients with celiac disease who may be candidates for non-dietary therapies. Drs Joseph Murray and Alessio Fasano reviewed clinical features and management challenges in adults and children with celiac disease.

The GFD is the only therapy for celiac disease, but effectiveness is limited by availability, expense, nutritional content, and attendant social isolation. Possible cross-contamination when dining out adds to difficulties with adherence. In addition, there is uncertainty about potential gluten exposure in medications and supplements. Social challenges of the GFD in the pediatric population include exposure risk in less-controlled settings, such as birthday parties, school lunch, and the transition to college. As a result, adherence is often imperfect. Dr Murray cited a questionnaire study of adults with celiac disease that found 70% of respondents reported inadvertent and/or intentional gluten consumption in the past 6 months.³ The constant vigilance required by this diet can be a source of great anxiety and can have substantial impact on adherence to treatment requirements.

Patients report persistent symptoms despite attempting to adhere to the GFD. Persistent or recurrent symptoms can be intestinal or extra-intestinal.⁴ Because symptoms tend to be nonspecific in nature, serologic markers, along with histology, can help define target patient populations whose symptoms are due to celiac disease. Persistently elevated tissue transglutaminase antibodies and persistent villous atrophy have been reported to correlate with gluten exposure, and the presence of these abnormalities indicates that symptoms are induced by gluten.⁵

Dr Murray stated that non-dietary therapies could be targeted to patients who have ongoing symptoms, despite attempting strict adherence to the GFD, but other patient populations could also potentially benefit. For example, recently diagnosed patients might benefit from a medication that accelerates both symptomatic improvement and healing of duodenal histology. Dr Murray also stated that asymptomatic patients could potentially benefit from a

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Abbreviations used in this paper: FDA, Food and Drug Administration; GFD, gluten-free diet; GI, gastrointestinal; HRQOL, health-related quality of life.

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medication that blocks gluten-induced mucosal damage, if the latter is established to increase risk of malignancy. Such a therapy might offer an extra degree of protection and be used in settings when the chance of gluten exposure is increased. Dr Fasano added that there might also be utility in treating asymptomatic children with celiac disease who are also affected by neurodevelopmental or behavioral conditions (such as Down syndrome), in whom judgment can be impaired regarding the long-term consequences to lack of dietary adherence. This “safety net” approach might be further applied to adolescents or other groups at increased risk of gluten exposure.

If a medication that protects against large amounts of gluten exposure, or even replaces the GFD, became available, patients who could benefit from such therapy would expand further. Children with the dual diagnosis of type 1 diabetes and celiac disease would particularly benefit from a medication that would allow for gluten exposure and protect against mucosal damage, given the arduous set of dietary restrictions of this dual diagnosis.

During the discussion period, concern was raised about the possibility of a “moral hazard,” wherein the availability of pharmacologic therapy could result in lapses in patients’ dietary adherence, much as the prescription of lipid-lowering drugs could lead to less-stringent dietary behavior for preventing cardiovascular disease. It is important to take into consideration and determine the level of gluten exposure that is considered safe while a patient is taking a pharmacologic therapy. Although most panelists believed that net harm due to excess dietary indiscretion is unlikely, target patient populations must be monitored and educated with practical and evidence-based dietary advice.

Session 2: Defining Clinical Benefit in Celiac Disease Trials Intended to Support Marketing Approval

The second session expanded these themes by defining the clinical benefit from the perspective of patients, adult and pediatric gastroenterologists, and the FDA. Speakers included patient representative Alice Bast; adult gastroenterologist Dr Sheila Crowe; pediatric gastroenterologist Dr Ivor Hill; and Dr Jessica Lee, Medical Team Leader, FDA Division of Gastroenterology and Inborn Errors Products.

Patients desire non-dietary treatments for celiac disease, which has been substantiated by survey studies.⁶ A recent study (presented at the 2016 Digestive Disease Week by Dr J. Tomal and colleagues) found that celiac disease patients are more interested in therapies that protect against gluten cross contamination than that allow for intentional gluten ingestion. For patients with celiac disease, a lifelong GFD is a medical prescription; a concept that has been somewhat diluted by the rise in gluten-free awareness at the expense of celiac disease awareness. Celiac patients define clinical benefit in a number of ways, such as decrease or absence of gastrointestinal (GI) and non-GI symptoms, improvement in

gut inflammation, or eating outside the home without having to think about their diet. While every patient might desire something slightly different, the overarching theme of clinical benefit from the patient’s perspective appears to be quality of life—free of symptoms and inflammation without worry about contamination.

In terms of a definition of clinical benefit, there was agreement among patients and clinicians at the workshop that patients with typical GI symptoms should be the focus of initial studies, as these symptoms are common, can be measured in a reasonable time frame, and are present in both children and adults. In a review of pediatric patients with celiac disease from Nationwide Children’s Hospital, 77% reported typical GI symptoms, while atypical and non-GI symptoms accounted for only 6% and 5% of patient symptoms, respectively (Ivor Hill, personal communication; February 29, 2016). Thus, studies assessing atypical and extraintestinal symptoms could pose enrollment challenges, especially in children. Using signs of the disease (eg, osteoporosis or anemia) as a measure of clinical benefit would require longer studies, as these conditions do not resolve quickly. As Dr Crowe summarized, “patients with celiac disease want to lead a normal life,” and the “lowest hanging fruit” for defining clinical response initially appears to be improvement in typical GI symptoms, with expansion to other measures thereafter.

The FDA’s perspective on clinical benefit is defined for any condition as “favorable effect on a meaningful aspect of how a patient feels, functions or survives as a result of a treatment.”⁷ As survival is not a pragmatic end point in celiac disease, the focus here is on measuring a meaningful aspect of how a patient feels and functions as a result of treatment. It was clear that when defining a meaningful clinical outcome in celiac disease, it is not “one size fits all.” Clinical benefit could be defined differently depending on the target population, the mechanism of action, and intended use of a pharmacologic agent. However, the FDA emphasized that a clear definition of clinical benefit and a reliable method of measuring benefit are key to designing both phase 2 and 3 trials in order to eventually support marketing approval.

During the public comment session, health-related quality of life (HRQOL) as a measure of clinical benefit for celiac disease was discussed. HRQOL encompasses the effect of illness and its treatment on physical, psychological, and social aspects of life. Dr Lee from the FDA discussed challenges in using HRQOL as a primary measure of clinical benefit, especially given heterogeneity in how one measures this concept. Some individuals suggested developing composite measures that include symptoms and HRQOL, as well as objective markers, such as serology and histology. Overall, consensus was reached that most common disease-related GI signs and symptoms that occur in the majority of patients are a reasonable starting point for defining clinical benefit for both adults and children, but it will be important to ensure (eg, using an objective measure) that signs and symptoms experienced by patients are indeed due to active celiac disease, because there is a large overlap between GI diseases.

Session 3: Measuring Clinical Benefit in Celiac Disease Trials Intended to Support Marketing Approval

The final session addressed issues on how to measure clinical benefit in trials supporting drug approval. This session covered metrics of treatment effect in celiac disease, including patient-reported outcomes, histologic assessment, and serologic tests.

The session began with an FDA perspective regarding clinical outcomes assessments by Dr Elektra Papadopoulos. The FDA must ultimately evaluate whether a new therapy improves how a patient feels, functions, or survives. Clinical outcomes assessments measure how an individual feels, functions, or survives, and include measures reported by clinicians, non-clinician observers, or patients. In celiac disease, key disease-related symptoms are one of the critical outcomes measures. Initial steps of end-point development include defining the disease, identifying symptoms that are most important to patients, and understanding how symptoms vary across individuals and are expected to improve with therapy.

There was consensus among patients and clinicians at the workshop that symptoms, in particular diarrhea and abdominal pain, will be central patient-reported outcomes for therapies aimed at improving symptoms. For pediatric patients with celiac disease who are too young to reliably self-report, observer-reported outcomes will be needed. The FDA Center for Drug Evaluation and Research's Guidance for Industry and FDA: Staff Qualification Process for Drug Development Tools allow external stakeholders to seek advice from the FDA in a precompetitive manner to develop and test drug development tools that are intended to be publicly available for use.

In addition to signs and symptoms, HRQOL was discussed, as it became clear that HRQOL is a major concern for both patients and clinicians. HRQOL in most GI disorders is driven almost entirely by symptoms, while for celiac disease, both disease symptoms and GFD contribute to the negative impact on HRQOL.⁸ The burden of trying to follow the GFD and anxiety surrounding asymptomatic gluten exposure was discussed. Questions were asked about the potential of making distress and anxiety related to following a GFD and asymptomatic exposures a basis for drug approval. The FDA acknowledged HRQOL as important. However, HRQOL is a broad concept that includes impacts of a disease that may not be modifiable. Additionally, because many confounders can impact the effects of a disease on patients' lives, it was argued that the greatest opportunity to demonstrate treatment benefit in celiac disease clinical trials is through signs and symptoms of the disease. FDA representatives reinforced that patient reported symptoms are appropriate end points for clinical trials, and that for a drug to be approved to relieve the distress of adherence to a GFD, the initial key end point would be to show that the drug allows gluten to be consumed without disease exacerbation. Similarly, for a drug to be approved with labeling that states that the drug was shown to reduce anxiety related to gluten exposures, the product would first have to

show that it eliminated the negative biologic impact of those exposures on the underlying disease.

The presentation on histology as an outcomes measure was given by Dr Benjamin Lebwohl. Small intestinal histology, either as a co-primary end point with symptoms or as a secondary safety end point, has a major role in clinical trials to evaluate potential therapeutics. Gluten exposure leads to reproducible changes in villous height to crypt depth ratio and intra-epithelial lymphocytes that makes histology very powerful as a primary outcome in gluten challenge studies.^{9,10} The utility of histology as a primary end point for studies of therapies adjunctive to the GFD intended to support drug approval was the focus of this session.

Potential issues with histology include invasiveness, expense, inter-observer variability, uncertainties about scoring mixed association with long-term outcomes,^{11,12} differences between kinetics of healing and kinetics of damage during gluten challenge,^{9,13,14} lack of evidence to support the degree of histologic improvement necessary to impart clinical benefit, and the poor correlation between severity of villus atrophy and severity of symptoms. Additionally, while quantitative histology, including villous height to crypt depth ratio and intra-epithelial lymphocyte count, has been used in clinical trials, quantitative histology is not available in clinical practice and, therefore, is not easily verifiable or interpretable by clinicians.

For these reasons, Dr Lebwohl suggested that, in adjunctive treatment studies, histology might be used for inclusion criteria to help ensure that ongoing symptoms are due to active celiac disease. As mucosal healing is not universal, uniform, or predictable, Dr Lebwohl concluded with the proposal that histology is difficult to use as a primary end point in adjunctive treatment trials, but should be measured, perhaps as a secondary qualitative end point with a minimum requirement to show a lack of worsening during the course of the trial.

The role of serology in assessment of clinical benefit was discussed by Dr Daniel Leffler. The 3 serologic tests most commonly used in celiac disease currently are endomysial antibody, transglutaminase, and deamidated gliadin peptide.¹⁵ Currently, the only FDA-cleared use for celiac serologies is as an aid for diagnosis of patients with suspected celiac disease. This limits how serologies can be used in regulatory trials, although they are routinely used for monitoring in clinical practice. To date, no manufacturer has submitted a claim for use of serology tests for disease monitoring, and the FDA is only able to review submitted claims.

Dr Leffler presented data to support that serologic tests can be used to predict histologic damage, osteopenia, and symptomatic response to a GFD.^{16–18} During gluten challenge, symptoms, histology, and serology are all responsive during different time periods (Figure 1). During gluten challenge, symptoms become maximally elevated within a few days and resolve quickly after gluten is withdrawn. In contrast, histology is significantly altered within 2 weeks, but celiac serologic tests do not become elevated for a month.⁹ This illustrates the difficulty in ensuring that symptoms in patients with celiac disease are due solely to

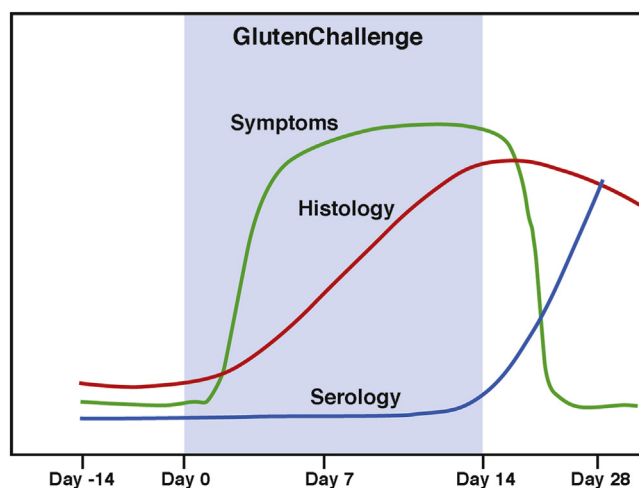


Figure 1. In patients with celiac disease, symptoms, histology, and serology are all responsive over different time periods during gluten challenge. (Adapted from Leffler et al,⁹ with permission.)

gluten exposure. In addition, there are currently no data evaluating the relationship between serology and long-term outcomes.

Dr Leffler stated that, despite these limitations, serologies can have major roles in clinical trials, and shared 3 scenarios where serologies might be useful. First, serologic tests could help define inclusion criteria. In gluten challenge studies, Dr Leffler stated that participants should have normal serologic titers in order to show deterioration with gluten exposure.^{19,20} Results from 2 adjunctive treatment studies are similar, with elevated transglutaminase in approximately 25% of enrolled symptomatic patients.²¹ Serologic titers were only modestly associated with histology and symptom severity, suggesting that limiting recruitment to patients with elevated serologies is neither feasible nor supported by existing data.²² Secondly, Dr Leffler stated that serologic tests might be used for enrichment or stratification of participants with different serologic levels to select populations most likely to benefit from therapy. Lastly, Dr Leffler stated that serologic tests might serve as an end point. While quantitative histology is the gold standard to assess celiac disease activity, serologies are noninvasive, widely available, and reflect immune activation. Given this, Dr Leffler stated that following serologies to ensure there is no increase over time is both important and feasible in larger trials, including post-marketing trials.

The talk on FDA clearance and approval of serologic tests was given by Julia Tait Lathrop, PhD, from the Center for Devices and Radiological Health. Dr Lathrop noted that regulatory requirements for device clearance or approval flow from the Intended Use/Indications for Use of the test. She also noted the risk of a device generally considers the risk of the harm to patient if the test result is wrong. Depending on how a test is used, a sponsor might need FDA approval of an Investigational Device Exemption before using a biomarker test in a clinical trial. For example, Institutional Review Board approval alone may be sufficient if a new test is only going to be used for research; however,

if a test is going to be used in a clinical trial, its use might require an Investigational Device Exemption.

Dr Lathrop also noted that celiac serologies have been cleared only as an aid in diagnosis of celiac disease; they have not been cleared as a replacement for biopsy, not for monitoring disease progression or drug response. Disease-monitoring studies can be challenging to design and perform because of the need to demonstrate a correlation between changes in the test result and clinically meaningful changes in a patient's condition. Investigators and device manufacturers were strongly encouraged to consult with Center for Devices and Radiological Health before starting a monitoring study using Center for Devices and Radiological Health's pre-submission process (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>).

This final talk was given by George Dukes, MD, representative of PhRMA. Dr Dukes noted significant obstacles, including absence of precedent product approval for celiac disease, as well as challenges in defining target populations for pharmacologic therapy, clinical end points, measurement tools, clinical and meaningful differences in responder criteria, lowest effective dose, and translation to the pediatric population. He noted that patients at this meeting expressed interest in improved "quality of life," both by lessening their symptoms and by decreasing the burden of the gluten-free diet. Dr Dukes stated that while preventing the immunologic response, reversing pathology and decreasing long-term disease morbidity are important goals, they may be difficult to achieve or prove at this stage. Another significant challenge is developing standardized non-invasive diagnostic tests for celiac disease that reflect disease activity with sufficient sensitivity to monitor therapeutic activity. Dr Dukes suggested that the field should work to develop a small number of instruments for use in therapeutic trials to estimate relative efficacy, and to develop common definitions for clinical meaningful response.

Finally, Dr Dukes suggested that it is important for industry to support fundamental knowledge of celiac disease, in particular, supporting epidemiology and pathophysiology as well as helping to facilitate diagnosis, identification of target populations, and potential targets for development of therapeutics. Specifically, he recommended support for development of a patient registry as a mechanism to better understand celiac disease and support therapeutic trials.

Discussion

There is reason to believe that celiac disease is entering a new phase, with recognition as a burdensome and morbid condition with a high unmet medical need for pharmacologic interventions beyond the GFD. While hurdles remain, participants at this first GREAT meeting that is specially geared toward celiac disease (third overall GREAT meeting) shared their vision regarding the need to better define target populations for pharmacologic therapies and measure clinical benefit in celiac disease trials. Finally, there was agreement from all participants that a collaborative

approach among patients, clinicians, industry, and regulatory bodies is necessary to improve the lives of individuals with celiac disease.

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Conflicts of interest

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