Regulatory and Clinical Expert Perspective of the 2022 FDA Draft Guidance "Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet"

The US Food and Drug Administration (FDA) has published the draft guidance "Celiac disease: developing drugs for adjunctive treatment to a gluten-free diet."[1] The guidance intends to promote clinical development of drugs and biologics for the treatment of celiac disease (CeD) as an adjunct to a gluten-free diet (GFD) in adults, based on current understanding of the natural history of the disease. A successful guidance document will promote robust evidence of meaningful benefit and lead to practicable, successful CeD drug development in clinical trials. Such trials should demonstrate improvement in how patients feel, function, or survive. However, we express a perspective about the recently published draft guidance that may help avoid failed or delayed drug development of effective celiac therapies.

Histologic improvement is absolutely a goal in the development of treatments for CeD. However, it will take years of phase II studies to develop sensitive histologic criteria to confirm clinically relevant histologic improvement and associated change in signs and symptoms. There are only small observational databases on histologic improvement beyond a year or 2 for patients on continued GFDs with complete healing uncommon beyond that point in patients with initial partial healing. This guidance is specifically drafted for those patients with continued symptomatic and histologic changes after at least a year on a GFD. This subset of patients is assumed to be intermittently exposed to lesser amounts of gluten, although this is not proven with certainty. To require evidence of histologic improvement as well as symptomatic improvement may well be an unachievable endpoint for studies at this point in time for this population with an important unmet medical need.

Defining Symptomatic and Histologic Remission as Endpoints in CeD Registration Trials

The current draft requires of a therapeutic that small intestinal histologic improvement is demonstrated within the context of a year-long study with an inclusion criterion of a GFD for 1 year. During this period, observational studies have demonstrated limited histologic responsiveness to a continued GFD in CeD.[2] However, there are no studies of any therapeutic that has improved histology beyond that achieved by a GFD. Whether a therapeutic can further improve histology in adults after a year of GFD or how long this process may take attests to gaps in the understanding of CeD. The limited trials of therapies for CeD that have successfully shown a beneficial effect on histology (protection from damage) have been short term and based on an exogenously ingested, predetermined quantity of a gluten challenge.

The FDA has sponsored 2 independent meetings to discuss the endpoints and clinical outcome assessments in CeD trials. The Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT) Workshop on Celiac Disease (GREAT III [2015][3] and GREAT VI [2021][4]) highlight the risk of requiring additional histologic improvement in the development of medical therapy in CeD.[2,3] A critical lack highlighted by experts in the field is a lack of current scoring systems considered valid for clinical trial purposes.[4] The guidance proposes use of a "clinically accepted scale" such as the Marsh-Oberhuber classification. The most current expert opinion specifically identifies this scale as inappropriate for use in clinical trial settings and has not been validated as desired by the FDA.[3–5] This fact is not referenced in the guidance. Published analysis of histologic disease activity indices for responsiveness, reliability, construct, and content validity has not provided the available instruments to offer the FDA a pathway for drug approval.[5]

What defines histologic change as clinically relevant and warranting an FDA-labeled indication for histologic improvement is not made clear in the current guidance. This issue has befuddled other mucosal diseases, including inflammatory bowel disease. The current FDA guidance confirms the regulatory risk by using unvalidated scoring systems for histologic change. Surprisingly, the guidance establishes the Marsh-Oberhuber histologic scoring system citing its "clinical acceptance" rather than validation by relevant FDA or external experts. Given the absence of acceptable histologic scoring systems and large knowledge gaps in what defines clinically relevant histologic improvement for therapeutics added to a GFD, there are potential negative consequences of failed studies for patients with CeD if the FDA requires evidence of histologic improvement for the first generation of approved therapeutics for CeD.

Mucosal healing is an important aspirational goal for celiac patients who follow a GFD but continue to experience symptomatic and histologic activity. The FDA should incentivize this goal of developing therapies that improve histology by including a specific therapeutic indication for mucosal healing in patients with residual evidence of histologic damage despite compliance with a GFD. However, CeD is clinically unique in the realm of inflammatory diseases of the digestive tract. Unlike other inflammatory conditions, once initial healing and symptom improvement on a GFD has occurred, clinically severe symptomatic flares do occur and effect health-related quality of life. The experts and patient presentations at GREAT VI described the impaired health-related quality of life experienced by patients with CeD, who despite their best efforts are exposed to gluten when not

in total control of their meal preparation using only unprocessed food. These flares are typically intermittent and begin shortly after an unintended ingestion of exceedingly small amounts of unidentified gluten and are not dependent on histologic changes. These symptoms do not typically persist beyond days after limited gluten exposure.

Preventing these symptoms is a clinically important benefit for patients. The eloquent description of the impact on socialization by patients at GREAT VI, reiterated by clinicians, highlights the important impact of a treatment that prevents symptom flares from unintended exposure and notes the lack of correlation between mucosal histology and clinically meaningful disease activity measures. Some of this discordance may relate to the differing time frames for resolution of symptoms (days) and development of histologic damage (months to years). Additional experts have also noted symptoms are poorly predictive of histology in nonresponsive CeD.[6]

Drug Development Is an Iterative Process

Requiring meaningful histologic improvement after initial healing over a year on a GFD after years of damage may delay development of therapies that offer symptomatic benefit. Studies that miss a histologic endpoint but trend in the right direction and succeed at meaningful symptomatic benefit should not be kept off the market. The results of such studies may inform the next generation of studies by providing data such as degree of histologic responsiveness to therapy, duration of study needed, and vital information about how to power such studies. We believe that robust symptomatic benefit associated with the stability to improved histology is a clinically meaningful basis for approval for the symptomatic treatment of CeD.

Although the entire CeD community agrees that histologic improvement is a vital goal of treatment, patients suffering from clinically important symptom flares are not benefited by requiring histologic improvement as the primary endpoint. The relationship of measurable but nonremission-inducing histologic improvement to symptomatic benefit as well as long-term outcomes are currently not established. A mandate for a co-primary endpoint including histologic remission is not clearly needed to define a clinical benefit for a patient and exceeds the regulatory definition of a clinical outcome needed for drug approval. Drug approvals have traditionally depended on the therapeutic agent's ability to improve how a patient feels, functions, or survives.[7] The FDA has the regulatory authority to ensure a positive benefit-to-risk assessment for each therapeutic at the time of a New Drug Application or Biologics License Application submission. A therapy that improves signs and symptoms at the expense of worsening inflammation would indeed not be a benefit for patients with CeD. We believe that the regulatory standard of drugs that can meaningfully improve CeD-related signs and symptoms is an important and valid basis for FDA approval at this time.

Additional Comments on the FDA Draft Guidance

The FDA is to be applauded for the flexibility in approach afforded to the endpoint requirements for symptom assessment. A valid endpoint must capture the core signs and symptoms and should not address only 1 symptom such as nausea or pain. The FDA guidance will ensure that endpoints used in phase III studies will capture meaningful change in clinical trials.

We find the FDA guidance on duration of study to be a conservative but appropriate approach given the potential moral hazard of increased gluten intake if a patient believes that a new therapy will allow him or her to ingest gluten intentionally. We agree with the minimum duration of study of 24 weeks for symptoms and 52 weeks for histology as required in the guidance. Given the variability in signs and symptoms over time and flares on a GFD, a longer duration than the typical 6–12 weeks is needed to capture a valid picture of what a chronic therapy has to offer a patient.

Conclusions

Drug development is an iterative process with FDA approved indications, usually expanding after initial drug approval. As studies of CeD treatments that include both histology and symptom endpoints generate results, we will advance our scientific understanding of how to study and define meaningful histologic improvement. The extent of potential histologic improvement, pace of change, determination of meaningful change, and translation into a meaningful effect size to power a study of superiority over a background of GFD are all predicates to the successful drug development that can provide adequate evidence of histologic improvement.

The FDA has drafted a guidance that includes much valuable advice on how to robustly study therapies for CeD. If, however, the proposed paradigm in this guidance had been used previously as the regulatory requirement for drugs to treat diseases with both structural and symptomatic components, many fewer effective and valuable drugs would be developed. Our current state of knowledge about the natural history of CeD supports a primary endpoint of meaningful improvement in symptoms with no worsening of histology.

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Conflicts of interest
The authors disclose the following: Lawrence Goldkind, Janice M. Soreth, and Andrew E. Mulberg are consultants for IMGX Inc, which is developing therapies related to celiac disease. Janice M. Soreth is a member of the Board of Directors of IMGX. Andrew E. Mulberg is also a consultant for Allakos, Protagonist, Digestive Care Inc, and Janssen.

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