EDITORIAL

Further Progress to Quantify Histological Damage in Patients With Celiac Disease

Celiac disease (CeD) is an inflammatory disease of the small intestine caused by dietary gluten proteins. Small intestinal histology of CeD is characterized by pre-infiltrative, infiltrative, hyperplastic, and destructive lesions that reflect time-dependent responses from a normal to a "flat" mucosa.[1]

In this issue of *Clinical Gastroenterology and Hepatology*, Syage et al present a novel algorithm that promises to advance exact quantification of histological damage in CeD.[2] CeD is an inflammatory disease of the small intestine caused by dietary gluten proteins. Manifestations range from severe gastrointestinal complaints, including malaise, malabsorption, and anemia, to mild intestinal or extraintestinal symptoms, including a range of autoimmune diseases.[3,4] CeD is common, with a prevalence of 1% to 2% in most countries of the world. Its pathogenesis is well-explored. Thus, certain gluten peptides that escape digestion are presented by HLA-DQ2 or -DQ8 on immune cells that reside in the intestinal lamina propria. This activates and expands gluten-specific CD4+ T cells that, in conjunction with activated CD8+ intraepithelial lymphocytes, cause mucosal remodeling from infiltrative to hyperplastic and destructive lesions.[1] Moreover, the enzyme tissue transglutaminase (TG2) modifies these gluten peptides by deamidation, which enhances their T cell activation potential and also serves as CeD autoantigen on which modern CeD serology is based.[5–7] CeD severity is also affected by genes other than HLA-DQ2/8, by the microbiota, luminal metabolites, and food constituents other than gluten.[8]

In contrast to impressive advances in serological screening for CeD, histology interpretation in daily practice has not progressed much beyond the atrophic concept since 1960.[9] Mucosal architectural remodeling[10] has erroneously been reported as atrophic changes, which contrasts with the definition and presentation of atrophy. Atrophy is defined as irreversible loss of tissue mass and function. Atrophic change of villus architectures in CeD has never been validated, as mucosal dysfunction like malabsorption and small intestinal inflammation are reversible with the gluten-free diet (GFD).[11] In his masterpiece, Marsh highlighted that "atrophic terminology is not only inappropriate but also seems to have paralyzed any new intellectual activity that might elucidate afresh the immunopathologic basis of the mucosal response to antigenic stimulation."[1] We recently demonstrated that sub-division of Marsh III has no practical value and precludes accurate assessment of CeD histology.[12]

The current study[2] introduces a novel histological score that is based on optimized histomorphometry, combining the 2 key parameters of mucosal damage in CeD (ie, villus height:crypt depth [Vh:Cd]), which is highly specific of mucosal remodeling once CeD has been established, and increased intraepithelial lymphocyte (IEL) counts that are sensitive indicators of intestinal inflammation. However, numbers of IEL lack specificity for CeD, because they can be increased due to other common (coexisting) etiologies like food allergy or viral/microbial infection. The authors showed, based on well-defined biopsies from 3 CeD drug trials, that the combined VCIEL (Vh:Cd + IEL) score had a higher predictive value for a therapeutic response than optimized Vh:Cd and/or IEL determinations alone. Notably, all biopsies were from patients with well-defined CeD who were biopsied at baseline (CeD in remission) and after a 6-week gluten challenge and treatment with or without a pharmacological therapy. These are ideal scenarios of clinical trials to demonstrate histological improvement with a given drug vs placebo.

A strict GFD is the basis of CeD therapy. Although it leads to improvement of symptoms and prevents further complications, up to 40% of patients on the GFD are not symptom-free, which is usually associated with lack of complete histological healing.[13,14] Moreover, the GFD is difficult to maintain in normal life, due to the presence of gluten in many seemingly gluten-free foods. This poses a risk of inadvertent gluten exposure in everyday life and contributes to patient anxiety and reduced quality of life. Therefore, therapies adjuvant to the GFD are needed and desired by many patients. With the advent of specific pharmacological agents for CeD[15] and the need for exact quantification of drug effects, an objective improvement of duodenal histology is key to clinical validation and final approval of a drug for CeD, along with improved patient-related outcomes.[14] To this aim, histomorphometry has been improved, including standardized morphometric analyses and minimization of inter- and intra-observer variation.[16–19] Therefore, VCIEL scores are best applied to patients in clinical trials. Thus, VCIEL scoring will likely be used in ongoing and upcoming phase II to III drug trials as an important secondary endpoint, to be further validated as a good indicator of drug efficacy.

A general problem with CeD histology, even with the optimized standardization and evaluation, is the modest correlation of mucosal remodeling with clinical severity. This is unavoidable despite the recommended 4 to 6 duodenal biopsies evaluated with well-standardized morphometry. One explanation for this may be more proximal vs more distal small intestinal lesions that could lead to an under- or overestimation of overall small intestinal damage. Thus, inflammation and

malabsorption may start before or after changes observed in conventional histology.[20] Poor orientation of biopsy samples may add to the discrepancies between clinical presentation and mucosal changes.[16] Here, increased IEL counts are a more dynamic and variable representation of injury than Vh:CD, although being less specific for CeD. However, in clinical study patients, follow-up histology will likely target comparable sites of the duodenum before and at the end of pharmacological intervention, which will increase the likelihood that changes of Vh:Cd and IEL counts in an individual patient can be more reliably assessed in such trials.

The VCIEL score is simple and can be calculated from existing standardized histomorphometry. The current VCIEL has given an equal weigh to the Vh:Cd ratio and IEL counts after their normalization to their standard deviations. The authors did not test if assignment of different weights to the 2 components could result in an even better predictive value over the presented VCIEL. Overall, VCIEL and its potential derivations may become a valuable tool to demonstrate efficacy of novel drugs on histological outcome in CeD.

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Conflicts of interest
This author discloses the following: Detlef Schuppan is principal investigator in studies CEC-3 and CEC-4 (TG2-inhibitor in patients with celiac disease), investigator in study Caly-002 (Calypso), and paid consultant to Falk Pharma, Immunic, Sanofi and Takeda. The remaining author discloses no conflicts.

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