Title

Management of Celiac Disease: Beyond the Gluten-Free Diet

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Management of Celiac Disease: Beyond the Gluten-Free Diet

See "Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease," by Lähdeaho M-L, Kaukinen K, Laurila K, et al, on page 1649.

Celiac disease is a chronic, small intestinal, immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals[1] estimated to affect ≤1% of the susceptible populations around the world. Currently, the only available management option is a life-long gluten-free diet[2]; however, the study from Finland by Lähdeaho et al[3] suggests that an oral glutenase to degrade small amounts of dietary gluten can attenuate gluten-induced small intestinal mucosal injury in patients with celiac disease who are consuming a gluten-free diet that contains small amounts of gluten. The need for a treatment above and beyond the gluten-free diet may seem less relevant at a time when gluten-free food products are far more available in stores and restaurants than ever before. However, the explosion of gluten-free offerings has created concerns for individuals who need to adhere to a strict gluten-free diet as treatment for celiac disease. Worldwide, there are varying standards of how much gluten can be present for a product to be deemed gluten free. Typically, the standard is measured as parts per million of gluten in food, which has been calculated based on what is thought to be a safe daily intake of gluten (10–50 mg/d) for those with celiac disease.[4] Depending on how much processed food a person consumes on a daily basis, the actual amount of gluten could be over this threshold for those who consume large amounts of gluten-free food. A greater problem is that most meals are consumed outside the home and relying on restaurants to provide truly gluten-free foods often leads to inadvertent gluten exposure. It is also inherently difficult to travel and maintain a gluten-free lifestyle. Thus, it is not unexpected that even the most fastidious celiac disease patients are exposed to gluten despite their best efforts.[5]

Voluntary compliance with the gluten-free diet is challenging owing to many factors, including the taste and texture of non-gluten alternatives, social reasons, peer pressure, and the inconvenience and expense of obtaining gluten-free foods (3–4 times more costly than their gluten-containing counterparts in the United States, Canada, and Great Britain).[5] A study presented at the 2012 Digestive Disease Week meeting assessing how patients viewed the effectiveness of various treatments indicated that patients with celiac disease rated a gluten-free diet as being more effective for their disease than did patients with other chronic diseases, such as dialysis for chronic renal failure or insulin injections for insulin-dependent diabetes.[6] Somewhat surprisingly, patients with celiac disease rated the burden of their treatment at or greater than the level experienced by individuals who needed dialysis, insulin injections, and other chronic medical treatments.[6]

A significant percentage of patients with celiac disease who are following a gluten-free diet may have persistent symptoms. The potential causes include continued gluten ingestion, often from trace ingredients not readily recognized as sources of gluten in food and from so-called hidden sources in non-food products such as medications and toothpaste. There is an increasing interest with an emerging literature about the factors that may be causing these symptoms, including fermentable starches, sensitivity to other grains often used in gluten-free foods, and the role of small intestinal bacterial overgrowth. Persistent celiac disease activity with elevated celiac disease–specific autoantibodies, inflammation, and/or villous atrophy is not unusual in patients taking an ostensibly gluten-free diet.[7,8] There are conflicting reports regarding whether such persistent mucosal injury is associated with increased mortality in patients with celiac disease.[9,10] Considering all these issues, other strategies beyond a strict gluten-free diet alone are highly sought after by patients with celiac disease.

Despite the promise of new treatments for celiac disease (Table 1), it is only relatively recently that clinical trials of new celiac disease therapies have been published.[11] At the time of writing this editorial, a search of "celiac disease treatment" in clinicaltrials.gov listed 81 studies. After excluding the 37 studies that were unrelated to celiac disease (eg, celiac plexus), of those that remained, only 20 studies focused on treatments for celiac disease beyond a gluten-free diet. Of those 20 studies, 14 have closed to recruitment, 4 are still open to recruitment, and 2 others are listed with an uncertain status regarding recruitment. Some other studies examine the effect of a gluten-free diet on conditions associated with celiac disease and a few trials focus on refractory forms of celiac disease.

Only a limited number of experimental therapies for celiac disease have been tested in randomized, controlled clinical trials. Larazotide acetate reduces the paracellular passage of gluten through the epithelial barrier into the lamina propria by inhibiting tight junctions.[12,13] The endopeptidase ALV003 reported in this issue[3] and in prior trials[14] and another endopeptidase, AN-PEP,[15] break down gluten to produce less or non-immunogenic peptide fragments. A therapeutic vaccine is being tested with the aim of developing tolerance to gluten.[11] Infection with the nematode *Necator americanus*[16] to shift from a Th1 to a Th2 milieu and treatment with a CCR9 antagonist have also been reported.[11]

In this issue of *Gastroenterology*, the latest study of a celiac disease treatment beyond the gluten-free diet reports the findings of a randomized, controlled, phase II clinical trial of ALV003, an oral mixture of 2 recombinant gluten-specific proteases in adult patients with biopsy-proven celiac disease.[3] The goal of the study was to test the ability of ALV003 to protect celiac disease patients from gluten-induced mucosal

Table 1. Treatments for Celiac Disease Beyond the Gluten-Free Diet

Types of Treatments	Status of Investigation
Intraluminally acting agents	
Lactobacilli to pretreat flours or dough	Preclinical
Transamidation of gliadin[19]	Preclinical
Prolyl endopeptidases	
ALV003[3,14]	NCT01255696,NCT00959114,NCT01917630,NCT00859391,NCT00626184
AN-PEP[15]	NCT00810654
Intraluminal polymers to bind gliadin (BL-7010)[20]	NCT01990885
Anti-gluten IgY oral passive antibody	NCT01765647 (not yet recruiting)
Study of humanized Mik-beta-1 monoclonal antibody (Hu-Mik-Beta-1)	NCT01893775
Inhibitors of transepithelial gliadin uptake	
Zona occludin receptor antagonist AT1001 (larazotide)[12,13]	NCT01396213,NCT01255696,NCT00620451,NCT00492960,NCT00889473, NCT00386165,NCT00362856
Modulators of the adaptive immune response	
Inhibitors of transglutaminase	Preclinical
Inhibitory gluten peptides	Preclinical
Blockers of HLA DQ	Preclinical
Immunomodulation	
Nectarus americanus (hookworm)[16]	NCT00671138
Gluten vaccine	NCT00879749
Regulation of T cells that home to the small intestine	
CCR9 antagonist	Preclinical
CCx282-B	NCT00540657

injury. The authors established the optimal daily gluten dose to be used in the 6-week gluten challenge study using 3 different doses: 1.5, 3, and 6 g of gluten were administered in 3 daily doses over a 6-week period. Based on results of histologic studies as well as patient tolerance, a dose of 2 g was selected. In the subsequent intervention study, adult patients with biopsy-proven celiac disease were randomized 1-to-1 to receive ALV003 or placebo drug along with the daily gluten challenge. 20 Twenty received the study drug and 21 received placebo. Analyses included measurements of villous height to crypt depth ratio, as well as numbers of intraepithelial lymphocytes, which served as primary endpoints. The gluten challenge led to mucosal injury in the placebo group; no significant mucosal changes were noted in the study drug group. Over the 6-week trial, there were significant differences in the morphologic changes that occurred between the 2 groups of subjects. All study subjects had celiac disease serology measured and 4 different instruments assessing quality of life and well-being, as well as gastrointestinal symptoms were assessed. No changes in celiac disease serology were seen between the 2 groups. Gastrointestinal symptoms secondary to gluten ingestion were significantly greater in the placebo group compared with those receiving active treatment. Overall, this study demonstrates that the use of 2 recombinant gluten-specific proteases reduces small intestinal mucosal injury owing to gluten ingestion in celiac disease patients receiving 2 g of gluten per day in an otherwise gluten-free diet. ALV003 contains a prolyl endopeptidase from *Sphingomonas capsulate*, in combination with another endopeptidase from germinating barley. AN-PEP, an endopeptidase from *Aspergillus niger,* was tested in a recent pilot study of 16 subjects demonstrating it was well-tolerated, but the primary endpoint was not met.[15]

There are some limitations to the current study, including the small sample size consisting of a homogenous population from Finland. It is somewhat surprising that serologic titers did not increase in the placebo group given that a 3 g gluten challenge for 2 weeks was shown to be sufficient to induce histologic changes in intestinal biopsies as well as increased titers of tissue transglutaminase immunoglobulin A.[17] Another pharmacologic approach to reduce the uptake of gluten from the intestinal lumen beyond a gluten-free diet is larazotide acetate, a described. In a study to evaluate the efficacy and tolerability of larazotide acetate in protecting against gluten-induced intestinal permeability and gastrointestinal symptom severity in patients with celiac disease,[12] the readout of permeability was sufficiently variable such that an accurate assessment of the effect of larazotide acetate on intestinal permeability was not possible. Some of the lower doses of larazotide acetate seemed to prevent the increase in gastrointestinal symptom severity induced by gluten challenge. A subsequent study of this agent[13] showed similar results despite a lack of effect on permeability. Interestingly, in that study all 3 study drug doses reduced symptoms from the 2.7-g gluten challenge over 6 weeks. In contrast with the current study of ALV-003, TTG IgA levels were reduced in all treatment groups compared with placebo.[13] The variation in results using 2 different agents, both intended to limit immunogenic gluten peptides from reaching the lamina propria, underscores the complexity of the mechanisms of celiac disease.

The potential of ALV003 and other therapies for celiac disease is significant given the ongoing exposure to low levels of gluten, persistent symptoms, and chronic intestinal inflammation, which may impact celiac disease morbidity and possibly mortality.[9,10] Should the ALV003 endopeptidase

come to market, there will likely be issues of availability and cost as a prescription treatment. Given the potential cost of endopeptidases and, for that matter, any new celiac disease therapeutic, who will be eligible to receive such new treatments? Individuals with celiac disease who eat out of their home, travel, and/or purchase prepared foods can never be completely certain of the gluten-free status of their food; as such, the majority with celiac disease could derive benefit from a treatment that reduces exposure to gluten and its potential harm. One can assume that only those with biopsy-proven celiac disease would qualify, whereas those with other forms of gluten sensitivity might not. This could alter emerging recommendations that the diagnosis of celiac disease can be achieved without performing small intestinal biopsies.[18] In an era when patients are often asked to use over-the-counter treatments in lieu of more expensive prescriptions, it seems likely that insurance plans will consider the gluten-free diet an over-the-counter agent and access to agents such as endopeptidases could be curtailed. Nonetheless, my patients and I look forward to the day when safe and effective therapies beyond a gluten-free diet are available to improve the health of those with celiac disease.

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Conflicts of interest
Dr Crowe served as the Principal Investigator of the UCSD site for the Alvine Pharmaceuticals, Inc, sponsored North American multicenter study, "ALV0003-1121, Clinical Evaluation of Three Celiac Disease-Specific Patient Reported Outcome Instruments in Established and Newly Diagnosed Celiac Disease Patients."

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