

Non-dietary forms of treatment for adult celiac disease

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Abstract

At present, treatment for celiac disease includes a strict gluten-free diet. Compliance, however, is difficult and gluten-free food products are costly, and, sometimes very inconvenient. A number of potential alternative measures have been proposed to either replace or supplement gluten-free diet therapy. In the past, non-dietary forms of treatment were used (*e.g.*, corticosteroids) by some clinicians, often to supplement a gluten-free diet in patients that appeared to be poorly responsive to a gluten-free diet. Some of new and novel non-dietary measures have already advanced to a clinical trial phase. There are still some difficulties even if initial studies suggest a particularly exciting and novel form of non-dietary treatment. In particular, precise monitoring of the response to these agents will become critical. Symptom or laboratory improvement may be important, but it will be critical to ensure that ongoing inflammatory change and mucosal injury are not present. Therapeutic trials will be made more difficult because there is already an effective treatment regimen.

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Key words: Adult celiac disease; Gluten-free diet; Non-dietary treatment of celiac disease; Tight junction inhibition; Protease; Immunotherapy; Vaccination

Core tip: Non-dietary forms of treatment for adult celiac disease are currently being evaluated and some have reached clinical trials. Some novel approaches being investigated include hydrolysis of gliadin peptides, inhibition of intestinal permeability, blockade of T lymphocytes and transglutaminase 2/human leukocyte antigen-DQ2 functions as well as induction of immune tolerance. Future evaluations will need to define effects on specific endpoints and ensure an improvement in symptoms, laboratory test results and, most important, mucosal inflammatory changes. Therapeutic trials with novel agents will be difficult from an ethical perspective as the current form of management with a gluten-free diet already provides an excellent result for most compliant patients with celiac disease. Finally, effects on other known superimposed diseases will need close evaluation (*i.e.*, lymphoproliferative and other malignancies).

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INTRODUCTION AND DIAGNOSIS

Celiac disease is a small bowel disorder that appears to respond clinically and histopathologically to a strict gluten-free diet. Indeed, the only universally accepted form of effective therapy for celiac disease is a gluten-free diet for life after the diagnosis has been accurately established.

Diagnosis involves demonstration of the following, ideally in a sequential fashion: (1) classical histopathological features of celiac disease shown in biopsies from the proximal small bowel; and (2) a response to a gluten-free diet^[1]. A very recent review and update on the prevalence, diagnosis, pathogenesis and treatment of celiac disease has appeared^[2]. Some, but not all clinicians, particularly those evaluating the pediatric age group, believe that serological testing (especially with tissue transglutaminase

antibodies) coupled with definition of human leukocyte antigen (HLA)-DQ2 and HLA-DQ8, rather than biopsy may be sufficient for diagnosis^[3,4].

Most patients present with diarrhea and weight loss. However, in recent years, more and more patients are now being detected with limited or no intestinal symptoms. In part, this reflects a greater appreciation by physicians for a widening spectrum of extra-intestinal changes associated with celiac disease and increased performance of screening using widely available serological markers (e.g., antibodies to tissue transglutaminase, or tTG). In addition, however, some recent studies have also suggested that there may be a very real increase in celiac disease even over the past decade or so, possibly related to some, as yet, unrecognized environmental factor^[5,6]. Typical biopsy changes include “flattening” of the villi with extension of the crypt epithelial cell compartment, increased numbers of plasma cells and lymphocytes in the lamina propria region, and increased numbers of intraepithelial lymphocytes. Although typical, these changes are not, in themselves, diagnostic as several disorders may mimic the changes of celiac disease^[7]. Only celiac disease responds to a gluten-free diet, although some symptoms, incorrectly attributed to celiac disease, may also respond to removal of gluten from the diet.

GLUTEN-FREE DIET AND COMPLIANCE

It is well known that life-long compliance to a gluten-free diet is difficult and expensive. In reality, a major problem underlying this form of prescribed diet therapy in celiac disease is complete removal of gluten since this substance is ubiquitous and present in many foods^[8]. Even foods that some authorities consider as safe, such as oats, may be contaminated with other grains that contain the injurious peptide sequences. The Food and Drug Administration in the United States has arbitrarily established a limit of < 20 ppm gluten (i.e., about 10 ppm gliadin) to be established as a “gluten-free” food. Total daily consumption of gluten also appears to be critical and some experts have estimated a threshold for some individuals with celiac disease to be lower than 50 mg daily^[9]. Even with these numerical considerations though, some patients with celiac disease may be even more sensitive, after only single ingestion of minute amounts of gluten. Even small amounts may provoke increased circulating levels of tissue transglutaminase antibodies and induce inflammatory changes in small bowel biopsies.

In recent years, a number of alternative dietary (e.g., genetically-modified gluten) and non-dietary approaches have been considered^[10-12]. Some are further detailed here including those already studied in some clinical trials as well as some that have not yet been evaluated. These might potentially serve, at least in part, in the future horizon for treatment of celiac disease. It is unlikely that any of these will be designated for independent treatment alone since the gluten-free diet, in spite of being difficult, costly and, often inconvenient, remains a highly effective

management approach.

GLIADIN PEPTIDE HYDROLYSIS

Some plants and micro-organisms express endoproteolytic enzyme activities that can hydrolyze the proline-containing gluten in foods to amino acids and smaller length oligopeptides that might permit later hydrolysis by human intestinal brush border enzymes. The prolyl-endopeptidases (PEP) are a family of enzymes with the ability to cleave internal proline residues in a proline-containing peptide^[13]. Even though PEP activity is expressed in the human small intestine, a gliadin peptide (i.e., 33-mer) that appears to be highly immunogenic is poorly hydrolyzed by human PEP^[14]. Other species, including some bacteria and fungi, express PEP activities and may, in theory, be very effective.

Aspergillus niger PEP can hydrolyze a number of gliadin peptides and its activity has been shown to inhibit the gliadin-induced immunologic response by gluten-specific T-cells^[15]. In a gastrointestinal model system, most hydrolysis appeared to occur in the stomach compartment with little activity required in the small intestine^[16]. Alternative PEPs from other microbial species (*Flavobacterium meningosepticum*, *Sphingomonas capsulata*, *Myxococcus Xanthus*) can hydrolyze gliadin peptides *in vivo* in the rat^[17,18], and pre-treatment of gluten with PEP appeared to reduce malabsorption of fat or carbohydrate in patients with celiac disease^[19].

Use of enzymes that involve other mechanisms could provide different treatment approaches. For example, specific proteases cleave storage proteins during germination of different grains and, as a result, may increase the rate of gluten degradation. A barley proteinase that hydrolyzes wheat gluten in rats has been reported to potentially provide protection against ingested gluten in gluten-sensitive rhesus monkeys^[20,21].

Additional studies have also suggested that different hydrolytic enzyme activities may be used in combination to improve efficiencies. For example, ALV003 consisting of PEP from *Sphingomonas capsulata* and a barley protease may prevent the T-cell response in patients with known celiac disease^[19]. In early clinical studies, orally-administered ALV003 was well tolerated without significant adverse effects^[22]. Phase 2 trials are in process and, have appeared in abstract form, suggesting possible benefit.

Alternative approaches to hydrolyze toxic gluten peptides have also employed enzyme mixtures isolated from germinating *Triticaceae*, including wheat, rye and barley. *In vitro* studies using intestinal epithelial cells and organ cultures of intestinal biopsies from untreated patients with celiac disease have demonstrated a reduction in markers of epithelial cell injury^[23].

Another suggested alternative to facilitate gluten degradation includes use of whole cultured bacteria. Normally, a complex microbial population is present in the intestinal lumen. A number of studies from different groups^[24,25] have described substantial quantitative and qualitative dif-

ferences in the intestinal microbiome of patients with celiac disease. More specifically, *bifidobacteria*, among several bacterial species, are reportedly abnormal in patients with celiac disease. *In vitro* cell culture studies as well as studies in animals have demonstrated reduced gluten toxicity and results of clinical trials are anticipated^[26,27].

Sequestration of gluten by polymeric binders acting in the intestinal lumen of patients with celiac disease could be a further alternative approach. Gluten may complex with linear co-polymers of hydroxyethylmethacrylate and sodium-4-styrene sulfonate to reduce toxic changes of gliadin induced in intestinal epithelial cells^[28]. In addition, this agent also reduced gliadin-induced alterations in barrier function and the numbers of immunoreactive cells, including intra-epithelial lymphocytes, in mice^[29]. Human effects of polymeric binders are not known, but the apparent limitation in side effects, low cost and potential for improved compliance compared to gluten-free diets is attractive.

INHIBITION OF INTESTINAL PERMEABILITY

The small intestinal mucosa in celiac disease is “leaky” with increased permeability. One of the proteins that contributes to permeability is zonulin. Larazotide acetate (*i.e.*, AT-1001) is a synthetic peptide derived from zonula occludens toxin of *Vibrio cholera*^[30]. It has been hypothesized to inhibit zonulin receptor binding to reduce the gliadin-induced increases in intestinal permeability. A phase 1 evaluation in treated celiac patients suggested that the medication was well tolerated, reduced intestinal permeability, decreased pro-inflammatory cytokine production and symptoms in celiacs after gluten exposure^[31]. A phase 2 evaluation showed a reduction in symptoms and autoantibodies. Added studies are needed^[32].

T-CELL LYMPHOCYTE BLOCKADE AND INHIBITION

Another broad category of agents being explored include agents that function to block key lymphocyte effects on the small intestinal mucosa. Specific antagonists as well as monoclonal antibodies that affect specific lymphokines are being explored^[33,34].

For example, gluten effector T-cells may be directed, at least in part, to the small intestinal mucosa by chemokine 25 and its receptor CC chemokine receptor 9. Blockade of this interaction by a selective antagonist has been hypothesized as a potential clinical approach in celiac disease.

Another suggested approach involves development of monoclonal antibodies, including anti-CD3, anti-CD20, anti-interleukin (IL)-10 anti-IL-15 antibodies^[33,34]. For example, reversal of mucosal damage in the small intestine of mice with overexpression of IL-15 could provide an

avenue for further evaluation.

TG2 AND HLA-DQ2 BLOCKADE

Several approaches may emerge for blockade of the adaptive immune response in celiac patients. One involves blockade of TG2 effects. TG2 enhances the binding of gliadin peptides to HLA-DQ2 and enhances T-cell activation in the small intestinal mucosa^[35]. Inhibition of *in vitro* TG2 activity inhibits gliadin-specific T-cell clones from celiacs. Similar inhibition occurs in the gliadin-induced proliferations of some, but not all (*e.g.*, CD8-positive lymphocytes) lamina propria lymphocytes and epithelial cells. Although TG2 is found in other tissues, TG2 inhibitors could theoretically provide a potential avenue for future therapy.

Another area of focus has been related to development of HLA-DQ2 blocking agents using gluten peptide analogues. These include both cyclic and dimeric gluten peptide analogues as well as gluten peptides with azido-proline residues substituted for proline. By changing the gliadin T-cell stimulatory sequence, conversion to an agonist or antagonist may result^[36].

IMMUNE TOLERANCE INDUCTION

In celiac disease, antigen-based therapy specific for a specific peptide sequence in gliadin might be an important future avenue of treatment. A peptide vaccine could promote tolerance by altering the effects of some immune-mediated cells involved in celiac disease pathogenesis. To date, however, definition of the precise antigen involved may not be sufficiently precise, to permit development of an effective vaccine for all celiac patients. A clinical phase 1 trial with Nexvax 2 peptide vaccine-containing a mixture of immunotoxic gliadins has been initiated^[37].

CONCLUSION

A number of avenues of treatment for celiac disease have been proposed as alternatives to a strict gluten-free diet. Some of these appear to be already advanced at the level of the bench in the laboratory, and even at the bedside in some clinical trials. At this time, there are still difficult issues that need to be addressed. First, the endpoint of any treatment regimen will require detailed evaluation. The gold standard is mucosal biopsy, but other forms of non-invasive evaluation require assessment to precisely define, not only the degree of responsiveness to a specific treatment regimen, but also the quality of the treatment response. For example, improved symptoms or improved laboratory parameters may signal an improved state, but if there is ongoing inflammatory change and mucosal injury, the treatment may not be a real advance in management and may still carry the long-term risks of only partially-treated celiac disease. Second, therapeutic trials will be difficult and, by necessity from an ethical

perspective, still require that patients with celiac disease be treated in both a treatment arm and the “placebo” arm with a known effective therapy, *i.e.*, gluten-free diet. At best, in spite of the burdens imposed on the celiac patient at present, the goal of these potentially new forms of therapy in celiac disease may predictably be to supplement the gluten-free diet in long-term management of celiac disease. Finally, the long-term effects of these therapies may not be immediately evident and require many years to define. In celiac disease, there appears to be an increased risk for some malignant diseases, including lympho-proliferative diseases, such as T-cell lymphoma^[58-40]. It is conceivable that some of these novel non-dietary forms of therapy may actually alter this background risk, especially over an extended period.

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