New and developing therapies for celiac disease

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***Abstract*:** The treatment for celiac disease, a removal of gluten in the diet, is safe and effective for the vast majority of patients. There is a large body of evidence that the diagnosis and treatment of those with celiac disease ensures considerable health benefits. Although a gluten-free diet is the principal treatment for celiac disease, it is relatively expensive, inconvenient and difficult to adhere to. For these reasons, there is interest in developing alternative therapies. Emerging research for the treatment of celiac disease has focused on three areas: to decrease gluten exposure, to modify intestinal permeability and to modulate immune activation. Therapies developed thus far consist of enzymes designed to digest gluten and the use of inhibitors of paracellular permeability to decrease the migration of gluten peptides into the lamina propria. Other potential therapeutic maneuvers include the binding of gluten by polymers, the use of tissue transglutaminase (TTG) inhibitors and DQ2 or DQ8 blockers, or modulation of cytokine production. While all represent new and exciting therapies, an ideal therapy should have virtually no side effects similar to a gluten-free diet. A pharmaceutical agent may be used on an intermittent basis, such as following occasional gluten exposure or on a chronic basis to mitigate the effects of potential inadvertent ingestion of gluten.

***Keywords*:** celiac disease, gluten, gliadin, prolyl endopeptidases, therapy

Introduction

Celiac disease is an autoimmune disorder resulting from exposure to gluten and a complex interplay of environmental and genetic factors [Green and Cellier, 2007]. While previously considered a rare condition diagnosed primarily in children with malabsorption, celiac disease has recently shown to be quite common. According to serologic population based studies, celiac disease may affect approximately 1% of the population [Green, 2007; Fasano *et al.* 2003]. Celiac disease has a worldwide distribution, detected not only in Europe and countries populated by Europeans, but also in North Africa [Ratsch and Catassi, 2001] the Middle East [Akbari *et al.* 2006; [Bitar *et al.* 1970] and India [Sood *et al.* 2006, 2001].

Current therapy – the gluten-free diet

The treatment for celiac disease is a gluten-free diet. This involves elimination of the grains containing gluten, wheat, rye and barley, as well as food products and additives derived from them [Green and Jabri, 2003]. Maintaining a gluten-free diet improves the health and quality of life for those with celiac disease, even in those with minimal symptoms [Casellas *et al.* 2008; Mustalahti *et al.* 2002]. Adherence to the diet improves symptoms [Murray *et al.* 2004] is believed to reduce the risk of malignancy [Holmes *et al.* 1989] and may reduce the risk of further autoimmune diseases [Cosnes *et al.* 2008; Ventura *et al.* 1999] though not all studies have demonstrated the latter [Viljamaa *et al.* 2005]. Other health benefits include improvement in bone mineral density, folate and homocysteine status and lipoprotein profile [Dickey *et al.* 2008; Brar *et al.* 2006a; Meyer *et al.* 2001].

Wheat is now consumed worldwide [Fasano and Catassi, 2001] and gluten is added to the regular diet in many and varied forms. Removal of exposure to gluten in the diet is safe and effective for the vast majority of patients. However, worldwide, adherence to the gluten-free diet is not uniform among those with celiac disease [Green and Cellier, 2007]. The highest rates of dietary adherence are reported for patients diagnosed at a very

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young age and those who were more symptomatic at presentation. Adherence to a gluten-free diet is improved in individuals with a thorough understanding of the diet and also those who participate in a celiac disease advocacy group [Leffler *et al.* 2008]. In France and Belgium, less than half of the adult patients who were studied strictly adhered to the diet for more than 1 year after diagnosis [Vahedi *et al.* 2003]. In the UK, compliance was low for both teenagers and adults [Kumar *et al.* 1988] and adolescents diagnosed via serologic mass screening in Italy had poor compliance [Fabiani *et al.* 2000]. Many diagnosed in childhood are not adhering to a strict gluten-free diet as adults [Bardella *et al.* 1994]. There are numerous reasons why there is low adherence to the diet. They include palatability, cost and availability, inadequate food labeling as well as social pressures and quality-of-life issues [Stevens and Rashid, 2008; Lee *et al.* 2007; Lee and Newman, 2003]. Due to cultural practices, certain ethnic groups may also have decreased adherence to a gluten-free diet [Brar *et al.* 2006b; Butterworth *et al.* 2004].

Approximately 7–30% of patients fail to respond to a gluten-free diet [O'Mahony *et al.* 1996] with the most common reason for continued symptoms on a gluten-free diet being the continued ingestion of gluten [Abdulkarim *et al.* 2002]. This may result from either inadvertent or intentional ingestion of gluten. Expert dietary counseling is vital for celiac disease patients and can improve compliance, though the availability of expert dietary counseling is limited [Nelson *et al.* 2007]. In addition nongluten containing grains are not fortified as is wheat flour. As a result patients on a gluten-free diet for 10 years or more were shown to be deficient in vitamins [Hallert *et al.* 2002]. In a recent study of patient perception of the burden of celiac disease and its treatment, many patients regarded it as a substantial burden with a quarter of screen detected patients reporting regret at being diagnosed [Whitaker *et al.* 2009]. On follow-up biopsy adults rarely have a normal duodenal biopsy compared to children [Lee *et al.* 2003; Selby *et al.* 1999; Dissanayake *et al.* 1974]. The reasons for this are unclear, however possible causes include the difficulty in totally removing gluten from the diet.

For many of the above reasons patients and their physicians see benefit in a pharmaceutical agent to help them with the gluten-free diet, or even allow the ingestion of gluten. The concept of the development of a pharmaceutical agent to treat celiac disease has become a reality because of the rapid expansion in the knowledge of the pathological mechanisms of the damage induced by gluten in celiac disease. Nondietary therapies have focused on three main areas: to decrease gluten exposure, to modify intestinal permeability and to modulate immune activation. These therapies are illustrated in Figure 1. Several agents have reached the clinical study phase.

Mechanism of injury in celiac disease

Gluten is the protein component of wheat, rye and barley and is poorly digested in humans secondary to its high content of glutamine and proline [Hausch *et al.* 2002; Shan *et al.* 2002]. As a result, high molecular weight peptides, such as the 33mer (a gliadin residue containing 33 amino acids), remain in the human digestive tract intact [Shan *et al.* 2002]. These high molecular gliadin peptides are particularly immunogenic [Qiao *et al.* 2004; Hausch *et al.* 2002]. Gliadin peptides cross the intestinal barrier by both active transport (transcellular) processes

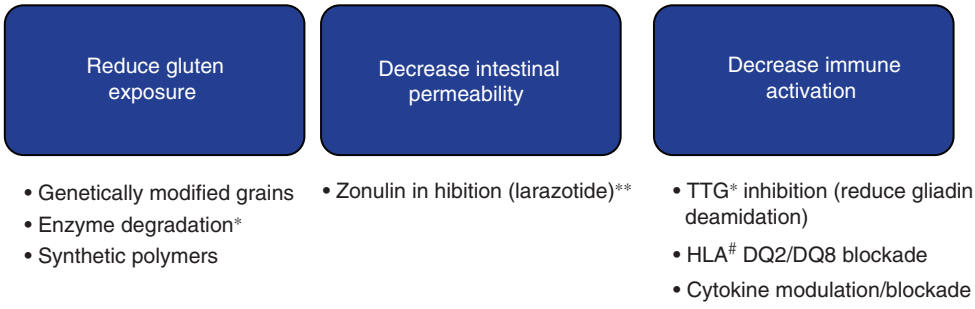

Figure 1. Developing celiac disease therapy. *TTG, tissue transglutaminase; **In human studies; #HLA, human leukocyte antigen.

[Bethune *et al.* 2009; Matysiak-Budnik *et al.* 2008] and via paracellular mechanisms [Lammers *et al.* 2008; Fasano *et al.* 2000]. Within the lamina propria, gliadin peptides are deamidated by the enzyme tissue transglutaminase [Molberg *et al.* 1998; van de Wal *et al.* 1998]. This enhances immunogenicity [van de Wal *et al.* 1998] by enabling a stronger interaction with human leukocyte antigen (HLA) antigen presenting cells in the lamina propria that express DQ2 or DQ8 molecules [Kim *et al.* 2004; Qiao *et al.* 2004]. This leads to T-cell proliferation and production of cytokines, particularly γ interferon that appears to perpetuate damage and influx of gluten [Bethune *et al.* 2009; Schumann *et al.* 2008].

Reducing gluten exposure

Genetically engineering grains to eliminate immunogenic gluten fragments would eliminate celiac disease. The large number of peptide epitopes located in different genetic loci of the wheat genome makes this approach challenging. Other potential challenges exist since the genetic modification of food is controversial and is not regarded favorably by the public. Another approach is the use of synthetic polymers that bind and neutralize gliadin. These have recently been studied and experimentally eliminate gliadin toxicity [Pinier *et al.* 2008].

A major approach that has been explored is the enzymatic degradation of the large, immunogenic gliadin peptides into small nontoxic fragments. This can be performed by prolyl endopeptidases (PEPs). These are proteases, found primarily in plants and microorganisms, able to degrade the proline-rich gluten peptides into smaller, less immunogenic fragments. This can be achieved by bacterial, or fungal enzymes that lend themselves to large-scale manufacturing [Stepniak *et al.* 2006; Piper *et al.* 2004]. Alternatively, probiotics have been demonstrated to degrade gluten and exert a protective effect on the damage exerted by gluten on cell cultures [Lindfors *et al.* 2008; De Angelis *et al.* 2006].

A technical concern is that the PEPs must not be inactivated, by the acidic milieu of the stomach. In addition, the bulk of gluten digestion should occur in the stomach. Groups in both the United States and the Netherlands have demonstrated efficacy of gluten digestion by different enzyme preparations [Gass *et al.* 2007; Stepniak *et al.* 2006]. To facilitate gluten degradation, a two-enzyme cocktail, consisting of a glutamine-specific cysteine protease derived from barley that has activity in the acid milieu of the stomach, and a bacterially derived PEP that acts in concert with pancreatic proteases for activity in the duodenum has been developed (ALV003, Alvine Pharmaceuticals Inc., CA) [Siegel *et al.* 2006]. The Netherlands group has developed a PEP preparation from *Aspergillus niger* (AN-PEP) with gastric activity [Stepniak *et al.* 2006].

Enzyme therapy is attractive because physicians are familiar with using enzyme preparations to treat lactose intolerance and pancreatic insufficiency. Therapy for celiac disease is however complicated because gluten must be completely prevented from interacting with the mucosa. Any remaining gluten peptides may lead to intestinal inflammation.

Decrease intestinal permeability

Another therapeutic target is to prevent the migration of luminal gluten peptides across the intestinal epithelium. The transport mechanisms involved are not completely understood but are considered to involve both transcellular and paracellular mechanisms. Intercellular tight junctions are altered in celiac disease. [Ciccocioppo *et al.* 2006]. Zonulin, an endogenous peptide involved in tight junction regulation, is amplified in celiac disease and increases intestinal permeability [Fasano *et al.* 2000]. Although the mechanisms of intestinal permeability and gliadin transport are not completely understood, potential therapeutic agents have been developed. AT-1001 (Alba Therapeutics Corporation, MD), a peptide that inhibits the action of zonulin, and the increase in intestinal permeability induced by gluten has been used in clinical studies [Paterson *et al.* 2007]. In a randomized, double-blinded, placebo-controlled study by Paterson and colleagues, subjects with celiac disease were challenged with gluten and given either 12 mg AT-1001 or placebo. Patients treated with AT-1001 had no increase in intestinal permeability while patients treated with placebo had a 70% increase. The patients treated in this study also experienced decreased gastrointestinal side effects and proinflammatory cytokine levels. The drug appeared to be safe and well tolerated [Paterson *et al.* 2007]. Further phase II studies are currently underway. The agent (AT-1001) is currently called larazotide.

Table 1. Therapeutic studies for celiac disease listed at the NIH website www.clinicaltrials.gov as accessed March 2009.

Status	Study
Completed	Safety and tolerability study of AT-1001 in celiac disease subjects Intervention: Drug: AT-1001
Active, not recruiting	Phase IIb study to study the efficacy of AT-1001 to treat celiac disease Interventions: Drug: AT-1001; Drug: placebo
Recruiting	Effect of *Aspergillus niger* prolyl endoprotease (AN-PEP) enzyme on the effects of gluten ingestion in patients with coeliac disease Interventions: Dietary supplement: *Aspergillus niger* prolyl endoprotease; dietary supplement: placebo
Completed	Inoculating celiac disease patients with the human hookworm *Necator americanus*: evaluating immunity and gluten sensitivity Interventions: Biological: *Necator americanus*; Other: Sham inoculation
Completed	A phase II study of CCX282-B in patients with celiac disease Interventions: Drug: CCX282-B; drug: placebo
Completed	Safety study of AT1001 to treat celiac disease Intervention: Drug: AT-1001
Recruiting	Randomized, double-blind, placebo-controlled study of larazotide acetate (AT-1001) in active celiac disease Interventions: Drug: larazotide acetate (AT-1001); Drug: larazotide acetate (AT-1001); Drug: placebo
Recruiting	A phase I study of the safety and tolerability of ALV003 in healthy adult volunteers and subjects with well-controlled celiac disease Intervention: Drug: 4 dose levels of ALV003
Active, not recruiting	Study of ALV003 in healthy adult volunteers and subjects with well-controlled celiac disease following a gluten-containing meal Interventions: Drug: ALV003; Drug: placebo

AT-1001, Alba Therapeutics Corporation, MD; AN-PEP, Stepniak et al. 2006; ALV003, Alvine Pharmaceuticals Inc., CA; CCX282-B, GlaxoSmithKline.

Decrease immune activation

While therapies currently being investigated aim to decrease the amount of gluten reaching the small bowel or its migration across the intestinal epithelium, another potential target of drug therapy is modulation of the immune response to gluten. This may be achieved by preventing gliadin deamidation through the inhibition of tissue transglutaminase, by preventing HLA presentation through blocking the HLA DQ2 or DQ8 molecules, or by modulating cytokine production. Other proposed therapeutic methods include vaccine development and immune modulation using hookworm. Hookworm infection may decrease gluten sensitivity in individuals with celiac disease via modulation of the immune response [Sollid and Lundin, 2009]. While some of these therapies are promising, they also may pose an increased potential for side effects.

There are several therapeutic studies currently underway as evidenced by the NIH website clinicaltrials.gov (http://clinicaltrials.gov/ct2/results?term=celiac+disease) these are shown in Table 1.

Conclusion

Although celiac disease is an autoimmune condition with a recognized environmental trigger, there is interest in developing nondietary therapies. Millions of people worldwide are affected by the condition and a large potential market exists for these agents. It is feasible that a new medication may be utilized. It is unclear whether these medications would be used continually to cope with inadvertent gluten ingestion, or intermittently, such as when an individual dines out of the home. There is potential that they may be used to mitigate the effects of intentional gluten ingestion. There are several challenges inherent in developing treatments for this condition. It has been difficult to develop an animal model to study celiac disease, though recently enzyme therapy was tested in a susceptible monkey model [Bethune *et al.* 2008]. Most studies have been conducted *in-vivo*, *ex-vivo*, and eventually in

small numbers of human volunteers. A drug must be resistant to degradation in the acidic environment of stomach as well as pancreatic and intestinal proteases and remain active in the small intestine. Objective endpoints are also difficult to define for therapeutic trials in celiac disease. Endpoints may consist of a combination of antibody levels, clinical symptoms, histologic scores, and functional assays of absorptive or permeability function. While useful, all of these approaches have limitations. The marked phenotypic variability in celiac disease makes the disease difficult to study.

Therapies to decrease gluten exposure, to modify intestinal permeability and to modulate immune activation, represent exciting emerging treatments for celiac disease, but a gluten-free diet is virtually without side effects. The gluten-free diet still represents the best and safest treatment for celiac patients. Once the diagnosis of celiac disease is established, the therapy is adherence to a gluten-free diet for life. Any new potential treatment must have a similar safety profile to the gluten-free diet. Clinical studies, consisting of 3 months duration, may not detect all side effects. Therapies resulting in increased infection, malignancy or severe gastrointestinal side effects would not be tolerated by clinicians or patients.

Conflict of interest statement

Dr Tennyson: none; Dr Lewis: none; Dr Green is on the Clinical Advisory Board of both Alba Pharmaceuticals and Alvine Therapeutics.

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