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REVIEW

Celiac disease: Alternatives to a gluten free diet

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Abstract

Celiac disease is a chronic inflammatory disorder of the small intestine caused by the ingestion of gluten or related rye and barley proteins. At present, the only available treatment is a strict gluten-exclusion diet. However, recent understanding of the molecular basis for this disorder has improved and enabled the identification of targets for new therapies. This article aims to critically summarize these recent studies.

Key words: Celiac disease; Gluten free diet; Therapeutic options

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INTRODUCTION

Celiac disease (CD) is a chronic inflammatory disorder precipitated in the genetically predisposed by the ingestion of gluten or related rye and barley proteins. CD is characterized by a spectrum of gastrointestinal and extraintestinal manifestations caused by inflammatory injury to the mucosa of the small intestine after the ingestion of gluten and by the activation of immune response[1]. Once considered a rare malabsorptive disease of childhood, CD is now recognized as a common condition (1:100)[2] that may be diagnosed at any age and that affects many organ systems.

Currently the only treatment for CD is life-long adherence to a gluten free diet. Complete removal of gluten from the diet allows the gut to recover, leading to normal food absorption. Even small amounts of gluten are enough to prevent recovery or cause further damage. Gluten contamination in gluten free products cannot be totally avoided; however, avoidance of gluten is essential for successful treatment. The accepted definition of "gluten-free products" by the Codex Committee on Nutrition and Foods for Special Dietary Uses is as follows: Gluten-free foods should not contain gluten higher than 20 ppm in total. Conversely, several other grains and starch sources are considered acceptable for a gluten-free diet. The most frequently used are maize, rice, and soya beans. Other grains generally considered suitable for gluten-free diets include tapioca, sorghum, carob, buckwheat, and millet. The main problem related to a gluten free diet is the acceptance of this dietary regimen. The most frequent cause of nonadherence to the diet is the poor palatability of gluten-free products. Additionally, misinterpretation of food labels, possible cross contamination, and insufficient education are commonly related to low compliance. In adult patients, adaptive and psychological aspects must be taken into account, particularly in patients without symptoms at the time of diagnosis[3]. Moreover, a gluten free diet has a large number of social and financial restrictions. Eating out, travelling, family life, and school or work environments are all challenging aspects of a celiac life[4]. Unfortunately, a gluten free diet cannot improve all disease-related disorders. In fact, all immunological disorders are poorly influenced by diet. It is clear that the use of a

"natural gluten free diet" leads to the greatest compliance and the lowest risk of nutritional imbalance.

The recent understanding of the molecular basis for this disorder has enabled the identification of targets for new therapies that are summarized in this review.

PATHOGENESIS AND THERAPEUTIC OPTIONS

Proline-rich gluten fragments are resistant to processing by luminal and brush-border enzymes and survive digestion[5] (Enzyme therapy) and are transported across the intestinal epithelium either paracellularly[6] (Antizonulin therapy), or intracellulary. Some gluten peptides directly induce mucosal damage *via* a non-T-cell-dependent pathway (Innate response)[7]. The best characterized peptide is the non-immunodominant p31-43/49 α-gliadin fragment that is thought to be unable to stimulate gluten-reactive CD4+ T cells. p31-43/49 induces interleukin 15 production in the celiac mucosa, which inhibits immune-regulatory signalling of transforming growth factor β, promotes dendritic cell maturation, and causes epithelial stress[8].

The α2-gliadin-33mer fragment, or immune-dominant peptide, is deaminated by tissue transglutaminase (tTg)[9] (Tissue transglutaminase inhibitors) and is then presented by dendritic cells (Peptides vaccines) to CD4+ T cells in the context of HLA DQ2 or HLA DQ8 molecules[10] (DQ2/DQ8 inhibitors**)**. Activated gluten-reactive CD4+ cells produce high levels of pro-inflammatory cytokines, thus inducing a T- helper cell type (TH1) pattern dominated by interferon gamma (INF γ)[11]. Additionally, activated CD4+ cells drive the activation and clonal expansion of B cells through the production of Th 2 cytokines, which differentiate into plasma cells and produce antigliadin and antiTg antibodies[12] (Cytokine therapy and selective adhesion inhibitor).

ENZYME THERAPY

An alternative to a strict gluten free diet may be coadministration of prolyl endopeptidases, which are endoproteolytic enzymes expressed by both microorganisms and plants. Some encouraging studies show that endopeptidases seem to be effective for reducing gluten toxicity. Supplementation of the rat brush-border membrane with trace quantities of a bacterial prolyl endopeptidase led to the rapid destruction of immunodominant epitopes of these peptides[13].

In another pilot study, celiac patients consumed a low dose of a gluten supplement daily (5 g, equivalent to one slice of bread) in the first stage and gluten pretreated with prolyl endoprotease (PEP) from flavobacterium meningosepticum in the second stage. Unfortunately, the results were inconclusive, mainly because of the measures chosen to demonstrate efficacy. Indices of fat and xylose malabsorption, but not histology, were used to measure the efficacy of the enzyme supplement. Using these malabsorption indices, the data showed that the therapy was ineffective in about half of the patients[14]. A recent study demonstrated the synergistic potential of two enzymes, a glutamine-specific endoprotease (EP-B2 from barley) and a prolyl endopeptidase (SC PEP from *Sphingomonas capsulata*), with respect to their ability to digest gluten before it reaches the intestine[15].

Another study determined the efficiency of gluten degradation by a post-proline cutting enzyme, *Aspergillus niger* (AN)-PEP, in a dynamic system that closely mimics the human gastrointestinal tract (TIM system). AN-PEP is capable of accelerating gluten degradation in a gastrointestinal system that closely mimics *in vivo* digestion. This implies that coadministration of AN-PEP with a gluten-containing meal might eliminate gluten toxicity, thus offering patients the possibility of occasionally abandoning their strict gluten-free diet[16].

ZONULIN ANTAGONIST

Fasano and co-workers first described the link between a *Vibrio cholera* toxin, zonula occludens toxin (ZOT), and a membrane receptor that induced an increase in intestinal permeability through a tight junction (TJ) re-arrangement[17]. Testing the hypothesis that ZOT was a bacterial homologue of an endogenous TJ modulator, they identified a 47KDa protein called zonulin. Similar to ZOT, zonulin also has the ability to link a membrane receptor and induce an increase in permeability[18].

Compared with healthy subjects, zonulin expression increases in the intestine of celiac patients prior to starting a gluten free diet[19]. The exposure of intestinal biopsies to gliadin in patients with CD will cause zonulin release. Gliadin, and at least two other peptides, bind the CRCX3 receptor on the enterocyte membrane, and zonulin levels increase in enterocytes through recruitment of MYD-88. Mucosal CXCR3 expression is elevated in active CD but returns to baseline levels following a gluten-free diet. Gliadin induces a physical association between CXCR3 and MyD88 in enterocytes. Moreover, gliadin increases zonulin release and intestinal permeability in wild-type but not CXCR3(-/-) mouse small intestine[6].

Following this hypothesis, attention was focused on AT-1001, which is an octapeptide inhibitor of paracellular permeability, whose structure is derived from the ZOT protein secreted by *Vibrio cholerae*. AT-1001 binds to zonulin and acts as a competitive agonist.

In 2007, AT1001 was used in an in-patient, double-blind, randomized placebo-controlled safety study using intestinal permeability indices. This showed a 70% increase in intestinal permeability in the placebo group, whereas there was no increase in permeability in the AT-1001 group. Interferon-gamma levels increased in four of seven patients in the placebo group, but only in four of 14 patients in the AT-1001 group. Gastrointestinal symptoms were more frequently detected in the placebo group than the AT-1001 group[20]. This pilot study encouraged a larger, currently ongoing study in which AT-1001 efficacy and safety are being tested by intestinal biopsy.

tTg INHIBITORS

Modification of gluten peptides by transglutaminase, especially deamidation of certain glutamine residues, is a key factor as the binding of modified peptides to HLA-DQ2 or DQ8 is enhanced, and T cell stimulation is potentiated. Therefore, inhibition of transglutaminase activity with highly specific enzyme inhibitors may represent a good therapeutic opportunity for CD[21].

DQ2/DQ8 INHIBITORS

Investigations into the molecular pathogenesis of CD have identified the major histocompatibility complex protein HLA-DQ2 as another potential pharmacological target[22].

Based on the HLA-DQ2 crystalline structure, Siegel and co-workers designed a different aldehyde-bearing gluten peptide analogue as a tight-binding HLA-DQ2 ligand and a reversible transglutaminase 2 inhibitor. No data are currently available on the *in vivo* efficacy and safety of such an approach. The aim is to develop a structure-based design of alpha-amido aldehyde containing gluten peptide analogues as modulators of HLA-DQ2 and transglutaminase 2[23].

OTHER THERAPEUTIC OPTIONS

Monoclonal antibodies to proinflammatory cytokines are another novel class of therapeutic agents being developed for the treatment of chronic inflammatory and other diseases.

Dietary gluten induces a response in the intestine of CD patients within a few hours. This is driven by high levels of proinflammatory cytokines, including IFNγ and IL-15, as has been thoroughly shown by gluten stimulation of biopsy explants. Il-15 is a key player in gluten-induced mucosa inflammation, as it is triggered by gliadin[24]. More recent *in vitro* studies suggest that the inhibition of interleukin-15 might have the potential to control CD. In fact, IL-15 induced in intestinal explants by gliadin shows a lower response threshold in celiac patients than healthy controls. This leads to the production of other immune mediators and the development of intestinal lesions, thus magnifying its effects within the intestine of patients with CD[25].

In Australia, a Phase I trial of a vaccine for CD was initiated in April 2009. The therapy involves repeatedly injecting solutions of gluten at increasing concentrations. The aim is to desensitize the subjects slowly, in a way similar to allergy desensitization treatments. The vaccine includes peptides accounting for a substantial proportion of the T-cell reaction to gluten in patients with HLA DQ2-associated CD. These peptides have been converted into a pharmaceutical agent capable of inducing immune tolerance in a rodent model of HLA DQ2-restricted T-cell immunity to gluten[26,27].

Other potential therapeutic options are based on use of the following antibodies[22-28]: (1) Anti-interferon γ antibody (fontolizumab)-downregulation of the TH1 mediated inflammatory response; (2) Human recombinant interleukin 10, (Tenovil)-interleukin-10 mediated expansion of type 1 regulatory T cells may suppress the immune response to gliadin; (3) Anti-CD3 antibody (visilizumab), anti-CD4 antibody (cMT412), anti-CD25 antibody (daclizumab) - gluten reactive T cells could be eliminated or made unresponsive by the administration of agents that alter the outcome of T cell activation; and (4) Anti-integrin α4 antibody (natalizumab), anti-integrin α4/β7 antibody (MLN-02), and integrin α4 antagonist (T-0047) - these inhibitors prevent leukocytes from migrating into inflamed tissues.

In conclusion, increasing knowledge of the inflammatory cascade triggered by gluten in genetically predisposed individuals will expand the possible alternative therapies to a gluten free diet.

REFERENCES

1 **Sollid LM**. Coeliac disease: dissecting a complex inflammatory disorder. *Nat Rev Immunol* 2002; **2**: 647-655
2 **Mearin ML**, Ivarsson A, Dickey W. Coeliac disease: is it time for mass screening? *Best Pract Res Clin Gastroenterol* 2005; **19**: 441-452
3 **Ciacci C**, Cirillo M, Cavallaro R, Mazzacca G. Long-term follow-up of celiac adults on gluten-free diet: prevalence and correlates of intestinal damage. *Digestion* 2002; **66**: 178-185
4 **Lee A**, Newman JM. Celiac diet: its impact on quality of life. *J Am Diet Assoc* 2003; **103**: 1533-1535
5 **Shan L**, Molberg Ø, Parrot I, Hausch F, Filiz F, Gray GM, Sollid LM, Khosla C. Structural basis for gluten intolerance in celiac sprue. *Science* 2002; **297**: 2275-2279
6 **Lammers KM**, Lu R, Brownley J, Lu B, Gerard C, Thomas K, Rallabhandi P, Shea-Donohue T, Tamiz A, Alkan S, Netzel-Arnett S, Antalis T, Vogel SN, Fasano A. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. *Gastroenterology* 2008; **135**: 194-204.e3
7 **Medzhitov R**, Janeway CA Jr. Innate immunity: impact on the adaptive immune response. *Curr Opin Immunol* 1997; **9**: 4-9
8 **Maiuri L**, Ciacci C, Vacca L, Ricciardelli I, Auricchio S, Quaratino S, Londei M. IL-15 drives the specific migration of CD94+ and TCR-gammadelta+ intraepithelial lymphocytes in organ cultures of treated celiac patients. *Am J Gastroenterol* 2001; **96**: 150-156
9 **Molberg O**, Mcadam SN, Körner R, Quarsten H, Kristiansen C, Madsen L, Fugger L, Scott H, Norén O, Roepstorff P, Lundin KE, Sjöström H, Sollid LM. Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. *Nat Med* 1998; **4**: 713-717
10 **Kim CY**, Quarsten H, Bergseng E, Khosla C, Sollid LM. Structural basis for HLA-DQ2-mediated presentation of gluten epitopes in celiac disease. *Proc Natl Acad Sci USA* 2004; **101**: 4175-4179
11 **Nilsen EM**, Jahnsen FL, Lundin KE, Johansen FE, Fausa O, Sollid LM, Jahnsen J, Scott H, Brandtzaeg P. Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. *Gastroenterology* 1998; **115**: 551-563
12 **Barone MV**, Caputo I, Ribecco MT, Maglio M, Marzari R, Sblattero D, Troncone R, Auricchio S, Esposito C. Humoral immune response to tissue transglutaminase is related to epithelial cell proliferation in celiac disease. *Gastroenterology* 2007; **132**: 1245-1253
13 **Hausch F**, Shan L, Santiago NA, Gray GM, Khosla C. Intestinal digestive resistance of immunodominant gliadin peptides. *Am J Physiol Gastrointest Liver Physiol* 2002; **283**: G996-G1003
14 **Pyle GG**, Paaso B, Anderson BE, Allen DD, Marti T, Li Q,

Siegel M, Khosla C, Gray GM. Effect of pretreatment of food gluten with prolyl endopeptidase on gluten-induced malabsorption in celiac sprue. *Clin Gastroenterol Hepatol* 2005; **3**: 687-694
15 **Gass J**, Bethune MT, Siegel M, Spencer A, Khosla C. Combination enzyme therapy for gastric digestion of dietary gluten in patients with celiac sprue. *Gastroenterology* 2007; **133**: 472-480
16 **Mitea C**, Havenaar R, Drijfhout JW, Edens L, Dekking L, Koning F. Efficient degradation of gluten by a prolyl endoprotease in a gastrointestinal model: implications for coeliac disease. *Gut* 2008; **57**: 25-32
17 **Fasano A**, Uzzau S, Fiore C, Margaretten K. The enterotoxic effect of zonula occludens toxin on rabbit small intestine involves the paracellular pathway. *Gastroenterology* 1997; **112**: 839-846
18 **Wang W**, Uzzau S, Goldblum SE, Fasano A. Human zonulin, a potential modulator of intestinal tight junctions. *J Cell Sci* 2000; **113** Pt 24: 4435-4440
19 **Fasano A**, Not T, Wang W, Uzzau S, Berti I, Tommasini A, Goldblum SE. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. *Lancet* 2000; **355**: 1518-1519
20 **Paterson BM**, Lammers KM, Arrieta MC, Fasano A, Meddings JB. The safety, tolerance, pharmacokinetic and pharmacodynamic effects of single doses of AT-1001 in coeliac disease subjects: a proof of concept study. *Aliment Pharmacol Ther* 2007; **26**: 757-766
21 **Dieterich W**, Esslinger B, Schuppan D. Pathomechanisms in celiac disease. *Int Arch Allergy Immunol* 2003; **132**: 98-108
22 **Sollid LM**, Khosla C. Future therapeutic options for celiac disease. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 140-147
23 **Siegel M**, Xia J, Khosla C. Structure-based design of alpha-amido aldehyde containing gluten peptide analogues as modulators of HLA-DQ2 and transglutaminase 2. *Bioorg Med Chem* 2007; **15**: 6253-6261
24 **Maiuri L**, Ciacci C, Auricchio S, Brown V, Quaratino S, Londei M. Interleukin 15 mediates epithelial changes in celiac disease. *Gastroenterology* 2000; **119**: 996-1006
25 **Bernardo D**, Garrote JA, Allegretti Y, León A, Gómez E, Bermejo-Martin JF, Calvo C, Riestra S, Fernández-Salazar L, Blanco-Quirós A, Chirdo F, Arranz E. Higher constitutive IL15R alpha expression and lower IL-15 response threshold in coeliac disease patients. *Clin Exp Immunol* 2008; **154**: 64-73
26 **Anderson RP**, van Heel DA, Tye-Din JA, Jewell DP, Hill AV. Antagonists and non-toxic variants of the dominant wheat gliadin T cell epitope in coeliac disease. *Gut* 2006; **55**: 485-491
27 **Bethune MT**, Borda JT, Ribka E, Liu MX, Phillippi-Falkenstein K, Jandacek RJ, Doxiadis GG, Gray GM, Khosla C, Sestak K. A non-human primate model for gluten sensitivity. *PLoS One* 2008; **3**: e1614
28 **León F**, Sánchez L, Camarero C, Roy G. Cytokine production by intestinal intraepithelial lymphocyte subsets in celiac disease. *Dig Dis Sci* 2005; **50**: 593-600

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