

Non-dietary methods in the treatment of celiac disease

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Prz Gastroenterol 2015; 10 (1): 12–17
DOI: 10.5114/pg.2014.47503

Key words: celiac disease, non-dietary treatment, AT-1001, prolylendopeptidases.

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Abstract

This is a selective review of the literature concerning the methods of celiac disease treatment, which can be an alternative to a gluten-free diet. The most advanced studies are devoted to the larazotide acetate (AT-1001, human zonulin inhibitor) and prolyl-endopeptidases degrading toxic gluten peptides (ALV003, AN-PEP). It is estimated that they will be registered within a few years. They will not become an alternative to the gluten-free diet but rather a supplement to it, which will enable patients to ease the nutritional restrictions.

Introduction

Celiac disease (CD) is a systemic disease of an immunological background, occurring in patients with a genetic predisposition. It is characterised by diverse clinical manifestations, the presence of specific antibodies in serum, the HLA-DQ2 and/or HLA-DQ8 haplotype, and enteropathy. The factor causing the disease is gluten – a plant protein found in wheat, rye, and barley [1].

The primary treatment of CD is currently a gluten-free diet. In most paediatric patients, the use of this diet causes an improvement or subsidence of clinical symptoms in several weeks, disappearance of serological CD markers within 6–12 weeks, and a remission of small intestine changes within 1–2 years. Strict adherence to the gluten-free diet results in a subsidence of deficiencies of microelements, macroelements, and vitamins and decreases the risk of autoimmune diseases and neoplasms associated with celiac disease. In approximately 4% of adult patients with CD the intestinal villi damage is sustained despite the elimination diet and in over 50% the increased intra-epithelial lymphocytosis is persistent [2].

Adherence to the gluten-free diet tends to be difficult. Gluten-free products are several times more expensive than their gluten-containing equivalents, and they are not freely available in all countries. Many patients tolerate gluten well in the amount of 34–36 mg/day. Only a sparse number of patients develop damage

of the mucous membrane of the small intestine [3]. Some patients are qualified as refractory CD patients and are resistant to the dietary treatment, while in fact, the sustaining clinical symptoms and/or intestinal villi atrophy in them is caused by the small amount of gluten contained in gluten-free diet. An application of a several-month-long gluten contamination elimination diet (GCED) allows for clinical and histological remission of symptoms, which is persistent even after transition to a normal diet [4].

Patients with a diagnosed CD have a clearly decreased quality of life compared to their healthy peers. This mainly pertains to the social aspects of life, and mostly to patients with adult-onset CD [5]. It is estimated that the percentage of patients strictly adhering to the gluten-free diet ranges between 42% and 91% (depending on the research method) and is lowest among ethnic minorities and patients with CD diagnosed in childhood [6].

Interest in therapeutic methods other than the gluten-free diet concerns most of the adult CD patients that were questioned, more frequently men, older than 50 years, eating in restaurants, unsatisfied with their body mass, and worried about the cost of dietary treatment [7].

Understanding the molecular mechanisms underlying the CD allowed for the identification of new therapeutic strategies, alternatives to a gluten-free diet. Such

strategies aim at three main pathogenic factors: the environmental factor (gluten), genetic predispositions, and abnormal intestinal permeability [8].

Genetically modified gluten

Currently, the gluten-free diet includes flour produced from rice, corn, sorgo, almonds, leguminous plants, soybean, *amaranthus cruentus*, buckwheat, brown rice, chia, chickpea, millet, quinoa, tapioca, teff, and other less popular crops. Unfortunately, most of them are poor in B-group vitamins and many other crucial nutrients. Also, they are devoid of the wheat's flavour. Therefore, genetically modified gluten of decreased immunogenicity is a potential therapeutic alternative for patients suffering from celiac disease [8].

Celiac disease is caused by the T-cell reaction to gluten proteins contained in wheat. Gliadin peptides are characterised by the presence of glutamine, an amino acid being a substrate for the tissue transglutaminase, which causes a deamidation of glutamine to glutamic acid. This reaction increases the gluten peptides' affinity for DQ2 and DQ8 by almost 100 times and causes strong induction of the gliadin-specific T-lymphocytes [8].

Gianfrani *et al.* [9] observed that blocking the glutamine residues at position 56-68 of α -gliadin with lysine methyl ester (Lys-CH₃) notably inhibits the immunological response of T-lymphocytes to immunotoxic peptides in patients with celiac disease. The modified peptides of gliadin have lower affinity to DQ2 molecules, which results in decreased interferon gamma expression by lymphocytes T. Modification of wheat flour with microbial transglutaminase, and lysine methyl ester eliminates the immunotoxicity of the digested food products. Transamidation of wheat flour with a food-grade enzyme and an appropriate amine donor can be used to block the T cell-mediated gliadin activity.

Spaenij-Dekking *et al.* [10] showed that, unlike most genes coding glutenin of high molecular weight and all genes coding α -gliadin, genes coding gluten proteins (α -gliadin, glutenin of low molecular weight) lack T-cell-stimulatory sequences. This implies that it may be possible to select types of crops that will not contain the α - and γ -gliadins, being toxic for CD patients.

Zonulin inhibitor

The discovery of zonula occludens toxin (ZOT) (an enterotoxin elaborated by *Vibrio cholera*, which rapidly, reversibly, and reproducibly opens tight junctions) has enhanced understanding of the mechanisms that regulate the intestinal epithelial paracellular pathway. Based on this knowledge, researchers were able to discover zonulin, which is a similar, endogenous modulator of

epithelial tight junctions. Gliadin is known to cause increased secretion of zonulin, which alters intestinal permeability, facilitates the transport of gluten, and triggers an inflammatory process characteristic of celiac disease or nonspecific inflammatory diseases of the intestines [8].

Larazotide acetate (AT-1001, Alba Pharmaceuticals) is an inhibitor of human zonulin, which stabilizes protein connections of the intestinal epithelium. This was confirmed both in vitro and in vivo in mice sensitized to gluten [11].

So far, several clinical trials involving larazotide acetate have been completed, including three phase-1 trials (two studies involving healthy patients and one involving CD patients) and phase-2 trials, with one of them still not published. In all first-phase studies the safety profile of larazotide acetate was comparable to that of the placebo [8].

Paterson *et al.* [12] studied 21 patients with CD in clinical and serological remission, who received 12 mg of AT-1001 or a placebo three times within three subsequent days, each time preceded by a gluten-containing meal eaten 30 min before the administration. Following gluten ingestion, a 70% increase in intestinal permeability was detected in the placebo group, while none was seen in the AT-1001 group. Interferon- γ levels increased in 57% of patients in the placebo group, but only in 29% of patients in the AT-1001 group. Gastrointestinal symptoms were more frequently detected in the placebo group when compared to the AT-1001 group.

In a study conducted by Leffler *et al.* [13] 86 patients with celiac disease controlled through diet were randomly assigned to larazotide acetate (0.25, 1, 4, or 8 mg) or placebo three times per day with or without gluten challenge (2.4 g/day) for 14 days. Variability of LAMA (urinary lactulose/mannitol excretion ratio) in the outpatient setting precluded accurate assessment of the effect of larazotide acetate on intestinal permeability. However, some lower doses of larazotide acetate appeared to prevent the increase in gastrointestinal symptom severity induced by gluten challenge. The preparation was well tolerated and no effects were observed.

In a double-blind placebo-controlled clinical trial 184 CD patients remaining on a gluten-free diet were treated with 1, 4, or 8 mg of larazotide acetate administered three times a day at a total daily dose of 2.7 mg of gluten for 6 weeks. The study Kelly *et al.* [14] showed that the preparation reduced the immunoreactivity caused by gluten (the concentration of anti-tissue transglutaminase and symptoms associated with gluten challenge). However, they did not find any differences in the lactulose-to-mannitol (LAMA) ratio – a marker of intestinal permeability.

The weak aspect of both studies was the use of urinary lactulose excretion as a marker for increased paracellular intestinal permeability of gliadin. According to Mazumdar *et al.* [15], a fluorescently marked gliadin would be a better marker for studying intestinal permeability than lactulose.

What limits the effectiveness of larazotide acetate inhibiting the paracellular transport of gliadin peptides is the transcellular transport of other gliadin peptides, which in the IgA complex are attached via the Tfr receptor to the surface of enterocytes and undergo transcytosis [16].

It is estimated that AT-1001 will be available within five years and will improve the life quality of CD patients by allowing them to eat gluten-containing food for the first time in years. Alba Pharmaceutical obtained permission from the Food and Drug Administration (FDA) to expand the study from just celiac disease to other autoimmune diseases, such as type 1 diabetes or Crohn's disease, which are also characterised by increased zonulin level.

Desensitisation therapy (therapeutic vaccines)

A promising direction of research on non-dietary treatment of celiac disease is the one concerning peptide therapeutic vaccines aimed at modifying the T-cell response. Currently, it is assessed that the studied vaccine may be effective only in CD patients with HLA DQ2 haplotype, i.e. in approximately 90% of patients [8].

Researchers from Nexpep in Australia have identified three immunogenic peptides of wheat, rye, and barley (gliadin, hordein, secalin) causing an immunological response in CD patients. A combination of these three key gluten peptides was included in the Nexvax 2 vaccine, which is currently being tested in a clinical trial. In a randomised, double-blind placebo-controlled study several different doses of the vaccine were used (9 µg, 30 µg, 60 µg, and 90 µg). They were administered intradermally once a week for 3 weeks to DQ2-positive CD patients strictly adhering to a gluten-free diet. In week three of the treatment the safety profile and vaccine tolerance were similar to those of the placebo. Patients receiving the highest doses of the vaccine suffered from gastroenterological symptoms (nausea, vomiting). This confirms that the vaccine can induce tolerance of gliadin peptides. The clinical symptoms and mobilisation of gluten-specific T-cells was similar after vaccine administration and oral administration of gluten in DQ2-positive CD patients strictly following a gluten-free diet [17]. The vaccine is currently being tested in Australia, New Zealand, and the USA [18].

Modulation of immune response by probiotic bacteria or nematodes

An interesting area of research on non-dietary treatment of CD are the attempts to modulate the immunological response through infecting CD patients with parasites and facilitating the Th-2-dependent immunological reaction, at the same time inhibiting the Th-1-dependent reaction induced by gluten.

A double-blind placebo-controlled 21-day study conducted by Daveson *et al.* [19] included CD patients strictly following the requirements of a gluten-free diet, who were intradermally vaccinated twice with larvae of a hookworm (*Necator americanus*; 10 larvae in week 0 and 15 larvae in week 12). In week 20 they were orally administered 16 g of gluten daily for 5 days. No differences were observed in the inflammatory parameters and the clinical and histological picture between the infected and non-infected subjects. The samples drawn from the infected patients showed decreased production of proinflammatory cytokines (IL-17A, INF-γ). However, no effect of infection was observed on the response of the anti-gliadin peptides lymphocytes. The justness of further investigation on hookworm infection in CD patients as an alternative to gluten-free diet is called into question, because no benefit in terms of symptoms was observed on clinical trials of this method.

Lindfors *et al.* [20] observed that adding two probiotic strains (*Lactobacillus fermentum* and *Bifidobacterium lactis*) to the cultures of small intestine epithelial cells could inhibit the damaging effect of gluten on the intestine. Probiotics can also accelerate the histological remission after the application of a gluten-free diet.

Oral enzyme supplementation

The gluten peptides, responsible for inducing the immunological response in CD patients, are rich in proline and are highly resistant to enzymatic proteolysis within the digestive tract. For many years there have been studies conducted to investigate the effectiveness of orally administered prolyl oligopeptidases in the degradation of toxic gliadin peptides before they reach the mucosa of the small intestine.

The 33-amino acidic peptide identified by Shan *et al.* [21], containing the epitopes that initialise the response to gluten in CD patients, can be degraded by the bacterial prolyl endopeptidase from the *Flavobacterium meningosepticum*. Researchers from Ireland found that the orally administered combination of bacterial and barley protease with endoprotease B isoform 2 degrades the gluten peptide to nontoxic fragments, which allows CD patients to ingest small amounts of gluten [22]. A similar effect was confirmed for prolyl endopeptidases from *Myxococcus xanthus* and *Aspergillus niger*.

In a pilot clinical trial, 16 CD patients in serological and histopathological clinical remission, following a strict gluten-free diet, were administered prolyl endopeptidase from *Aspergillus niger* (AN-PEP, DSM Food Specialties, Delft, the Netherlands) or a placebo, together with a gluten-containing meal (7 g, twice within 2 weeks). At phase 1 of the study, AN-PEP was well tolerated by the patients. No significant serological differences were observed during phase 2 of the study (lack of antiendomysial antibodies). Also, there were no histopathological differences (no changes in the histopathological picture of the intestinal mucosa). The results pertained to both groups of patients [23].

In a study by Siegel *et al.* [24] a mixture of two proteases (PEP from *Sphingomonas capsulata* and endoprotease B isoform 2 of cysteine from sprouting barley seeds (ALV003, Alvine Pharmaceuticals) was administered to patients in the form of a powder dissolved in water. ALV003 was dosed at escalating dose levels by cohort (100, 300, 900, and 1800 mg) and administered using a nasogastric tube directly after a meal containing 1 g of gluten. 300 mg of ALV003 degraded over 80% of the ingested gluten, and 900 mg protected against the damage of the intestinal mucosa within the 6-week gluten challenge.

In order to avoid the influence of low pH in the stomach on the activity of PEPs, it is recommended that they are produced in a form of enteral capsules. However, ideally the optimal degradation of gluten should take place in the stomach to limit the immune response in the proximal small intestine. Attempts to create covalent connections of prolyl endopeptidases with polymers are being made with the aim of increasing the stability of enzymes in low gastric pH [25].

Transglutaminase inhibitor

Human transglutaminase plays a crucial role in the pathogenesis of celiac disease. The enzyme catalyses the deamidation of gluten peptide-bound glutamine residues, thanks to which their affinity to the HLA DQ2 and HLA DQ8 receptors increases. There are three classes of TG2 inhibitors that differ based on their mechanisms of action: competitive amine inhibitors, reversible inhibitors, and irreversible inhibitors. Competitive amine inhibitors inhibit TG2 activity by competing and blocking substrate access to the active site without covalently modifying the enzyme. A crosslink is formed between the natural glutamine substrate and the competitive amine inhibitor. The irreversible TG2 inhibitors link irreversibly with the enzyme by covalently modifying it [8].

In an *in vitro* and *ex vivo* study, Rauhavirta *et al.* [26] showed that two inhibitors of TG2 (R281 and R283)

evinced protective effects for the intestinal epithelium exposed to gliadin.

However, severe side effects of the non-selective TG inhibitors may occur, since the TG is an omnipresent enzyme, and the amino acid sequence in the intestinal TG2 is similar to the one occurring in other human TGs. The TG2 deficiency is associated with the development of splenomegaly, autoantibodies, and immune complex glomerulonephritis in mice [27].

Recently, three highly soluble TG inhibitors have been discovered (ZED1098, ZED1219, ZED1227) showing high selectivity for intestinal TG2. The aim is to produce an inhibitor that, while passing through the mucosa, could obtain at the lamina propria of the mucosa a sufficient concentration at the lowest possible systemic activity. It should also be noted that some gluten peptides are immunogenic without deamidation by tissue TG. Therefore, combining them with other pharmaceuticals should be considered [28].

Polymer connectors

Polymer connectors are used in the sequestration of gluten in the digestive tract. In a study by Pinier'a *et al.* [29] P(HEMA-co-SS) (poly(hydroxyethylmethacrylate-co-styrene sulphonate) reduced digestion of wheat gluten and barley hordein *in vitro*, by decreasing the formation of toxic peptides associated with CD. In gluten-sensitised mice, P(HEMA-co-SS) reduced paracellular permeability, normalised anti-gliadin immunoglobulin A in intestinal washes, and modulated the systemic immune response to gluten in a food mixture. Incubation of P(HEMA-co-SS) with mucosal biopsy specimens from patients with celiac disease showed that secretion of tumour necrosis factor- α was reduced in the presence of partially digested gliadin. The copolymer was safe, active regardless of the pH of the environment, and the systemic exposition at oral administration was minimal.

Anti-inflammatory therapy

Modulation of inflammatory reaction can be achieved thanks to the activity of glucocorticoids and biological therapy. Budesonide, a glucocorticoid of a low bioavailability, has proven to be clinically effective in refractory and non-refractory celiac disease. Unfortunately, budesonide is effective in the distal small intestine, while in the case of celiac disease its action mainly in the proximal section is crucial [8].

Understanding the issues concerning some post-inflammatory cytokines and chemokines (TNF- α , IFN- γ , IL-15, CCL25, and CXCL10) in the pathogenesis of CD brings hope that there is a possibility to use biological therapy in the treatment of this disease. Unfortunately, the effectiveness of most biological pharmaceuticals

has not been studied so far in patients with CD. Some of the drugs that have been tested for other diseases (monoclonal antibodies against IL-15 in rheumatoid arthritis) have been disappointing [30]. Costantino *et al.* [31] showed that monoclonal antibodies against TNF- α are effective in the treatment of CD resistant to gluten-free diet after ineffective glucocorticoid therapy. However, the high cost and possible severe side effects may disqualify them as a possible drug for CD.

Eksteen *et al.* [32] showed that the low molecular selective antagonist of the CCR receptor for human chemokine CCL25 (GSK-1605786, CCX-282, Traficet-EN, ChemoCentryx, GlaxoSmithKline) selectively inhibits T- and B-cell entry into the small intestine while leaving the immune function at other anatomical sites unaffected.

A gluten-free diet is still the only medically accepted treatment for celiac disease. The most advanced studies are devoted to the larazotide acetate (AT-1001, human zonulin inhibitor) and prolyl endopeptidases degrading toxic gluten peptides (ALV003, AN-PEP). It is estimated that they will be registered within a few years. They will not become an alternative to the gluten-free diet but rather a supplement to it, which will enable patients to ease the nutritional restrictions.

Conflict of interest

The authors declare no conflict of interest.

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Received: 4.11.2013

Accepted: 17.02.2014