Title: Challenges to drug discovery for celiac disease and approaches to overcome them

Abstract

Introduction: The only available effective treatment for celiac disease is strict and long-term compliance with a gluten-free diet. Dietary gluten restriction must be strict and long term, but is difficult to achieve in many cases and alternative dietary strategies have been investigated in the past few years.

Areas covered: This review highlights the progress that has been made in the development of new therapeutics for CD. Detailed information of the evidence about the targets of the drugs related to their mechanisms of action is covered. The therapies are classified in five mechanisms: modification of gluten, intraluminal therapies, immunomodulation, intestinal permeability and modulation of adaptative response. The actual development phase and future approach are also described and discussed.

Expert opinion: There are several limitations in each of the treatment targets related to their complications or the lack of complete response to normal gluten containing diet. The most desired therapy for celiac patients is the induction of gluten tolerance that would be curative. Therefore, it is expected that shortly, alternative or complementary tools for the treatment of gluten-free diet will be available to patients with celiac disease and will improve their quality of life.

Keywords

Celiac Disease, gluten tolerance, immunomodulation, proteases, tissue transglutaminase, Intestinal permeability.

1. INTRODUCTION

Celiac disease (CD) is characterized by an immune-mediated sensitivity to gluten. It is considered to be a multifactorial disorder with a broad spectrum of symptoms and intestinal villous alterations that include lymphocytic enteritis and mucosal atrophy [1]. The prevalence of CD in developed countries is approximately 1% [2]. However, the currently available serology-based diagnostic techniques (antigliadin, anti-transglutaminase, and antiendomysial antibodies) may lead to misdiagnosis of some cases [3, 4]. For this reason, several strategies have been developed in the past few years to optimize the early diagnosis of CD in higher-risk groups [5, 6, 7, 8].

Gluten is a protein that is insoluble in both water and diluted salt solutions [9]. This protein triggers intestinal inflammation mediated by the human leucocyte antigen (HLA) system via HLA-DQ2 or DQ8 molecules. Intestinal inflammation may lead to the malabsorption of nutrients, as well as secondary iron deficiency (anemia) and osteoporosis.

The only available effective treatment for CD is strict and long-term compliance with a gluten-free diet (GFD). Nonetheless, it has been shown that mucosal recovery can be lengthy. Moreover, 30%–50% of patients have persistent lesions in the intestinal mucosa and recurrent symptoms despite dietary gluten restriction (GFD-resistant CD or non-responsive CD) [10, 11]. Gluten restriction requires extensive personal effort, which has psychological and social consequences and may limit full compliance [12, 13]. Unintentional or deliberate non-compliance with GFD occurs in up to 50% of cases [14, 15]. In addition, approximately 1% of patients with celiac disease do not respond to GFD (refractory CD [RCD]). These patients are diagnosed mainly in adulthood after long-term exposure to gluten and are at risk of developing complications such as RCD type II (an intestinal lymphoma) or its more severe complication, enteropathy-associated T-cell lymphoma (EATL) [16, 17].

2. PATHOGENESIS OF CD

CD develops in genetically predisposed individuals as an immune response to gluten present in certain grains (wheat, barley, and rye [18]). Although oats are considered safe for patients with CD, different oat varieties have distinct immunogenic potentials in patients with celiac disease based on the presence of toxic prolamines [19]. The immune system involves innate responses (caused by the direct toxic effects of gluten on the epithelium) and adaptive or specific

responses (via $CD4^+$ T lymphocytes in the lamina propria or underlying tissue). These responses are complementary and may result in damage to the intestinal mucosa [20].

Some gluten fragments, including α-gliadin, trigger an innate, toxic, and acute immune response not associated with T lymphocytes or HLA-DQ2/8 antigens [21, 22, 23]. Gluten causes oxidative stress through the production of nitric oxide via the activity of nitric oxide synthetase (iNOS) in intestinal epithelial cells [24, 25, 26, 27] and induces the expression of ligands such as MICA [28] in these cells. Gliadin can also directly disrupt the intercellular junctions between enterocytes [29, 30, 31]. However, the primary inflammatory mechanism involves the secretion of IL-15 by intestinal epithelial cells subjected to stresses [32]. This pro-inflammatory cytokine induces the expression of NKG2D in adjacent intraepithelial lymphocytes, causing apoptosis in MICA-bound intestinal epithelial cells, leading to villous atrophy [33, 34]. Epithelial cytotoxicity, together with the weakening of intercellular junctions, favors an increase in intestinal permeability, increasing the access of dietary gluten to the lamina propria, thereby triggering a local adaptive response.

The adaptive immune response is antigen-specific and is mediated by T-cells after antigenic presentation by antigen-presenting cells (APCs) carrying HLA-DQ2 or DQ8 molecules [35]. Macrophages and dendritic cells (DC) are the main APCs in the lamina propria and are increased in active celiac lesions [36]. These APCs are activated by IL-15 [35, 37, 38, 39] and are responsible for presenting gluten antigens, such as α-gliadin, to naive T lymphocytes in the lymph nodes via HLA-DQ2/8 molecules [37, 40, 41, 42] after the modification of α-gliadin by the enzyme transglutaminase 2 (TG2) [43, 44]. Following antigen presentation, $CD4^+$ T-cells become antigen-specific and migrate to the lamina propria where they respond to gluten through the secretion of pro-inflammatory cytokines (IFN-γ, TNF-α, and IL-18) and decreased production of regulatory or anti-inflammatory cytokines (IL-10 and TGF-β) [45, 46]. This pro-inflammatory activity is associated with tissue remodeling events, including crypt hyperplasia typical of CD, intestinal villous atrophy, and the activation of B lymphocytes, which stimulate the production of antibodies [35, 47]. In summary, gliadin has a dual effect in the intestine of patients with CD, and the activation of the innate immune response is essential for triggering the adaptive response in genetically susceptible individuals [48, 49, 50, 51, 52, 53].

3. NEED FOR NEW NON-DIETARY THERAPIES

The only effective treatment available for CD is long-term compliance with a GFD. Dietary compliance has been shown to be a safe and effective therapy; however, it is neither ideal nor highly effective in clinical practice. In adults with CD, daily consumption of small amounts of gluten (50 mg) for 3 months may cause damage to the small intestine [54]. Therefore, dietary

gluten restriction must be strict and long term, but is difficult to achieve in many cases. For example, the production and distribution of gluten-free foods are complex, which makes the final product more expensive than the equivalent non gluten-free food, and are consequently not achievable in all countries. In addition, a frequently cited limitation is the unpleasant taste and texture of gluten-free foods, which reduces flavor and consumption. In addition, cross-contamination with other food products may occur. Hence, unintentional dietary compliance is common [55]. Therefore, the current therapy significantly affects the psychological and social outcomes and the quality of life of individuals with CD [56]. In addition, the lower proportion of whole grains and fibers in gluten-free products and the higher consumption of refined carbohydrates have increased the rates of hepatic steatosis, coronary syndrome, and cardiovascular events [57, 58]. The European Union (EU) Ordinance No. 828/2014 of July 30, 2014, has established the norms to determine the quantity of gluten in food products. In EU countries, foods with less than 20 ppm of gluten are labeled as gluten-free [59], even though the threshold to trigger symptoms varies for each individual [60, 61]. This may explain why only 50% of individuals with CD adhering to a GFD achieve complete recovery of the duodenal mucosa. The unintentional or deliberate consumption of gluten is the leading cause of poor intestinal immune response [62].

A study conducted in the United Kingdom found that 40% of individuals with CD were unhappy with the GFD [63] because of the imposed dietary and social restrictions, higher cost, and poor taste of products. All participants were interested in other treatments, with vaccination considered the preferred strategy [63]. In addition, in many cases, compliance with GFD is difficult and costly, which leads to poor compliance and, ultimately, to poor clinical outcomes with the persistence of the existing symptoms [64, 65].

In summary, although full compliance with GFD is the main therapy for CD, the need to develop new, alternative long- and short-term dietary therapies is evident to i) promptly restore mucosal integrity in the diagnostic phase ; ii) allow short-term non-compliance in some cases (e.g., during travel and social events); and iii) improve clinical and social outcomes for patients with CD. For these reasons, alternative dietary strategies have been investigated in the past few years. The different non-dietary strategies are grouped according to the therapeutic objectives in Table 1.

4. **THERAPIES BASED ON THE MODIFICATION OF GLUTEN**

a) GENETICALLY MODIFIED WHEAT STRAINS AND

Lower exposure to dietary gluten may reduce the risk of the onset of CD [66]. The wheat strains used to date can be more immunogenic than ancestral or wild strains such as tritordeum or *Triticum monococcum* [67, 68, 69]. Therefore, the genetically-engineered diploid wheat strains that have no (or only small amounts) of immunogenic gluten peptides are potentially useful for patients with CD.

One possibility is the selection wheat strains with a reduced content of immunogenic epitopes, such as hexaploid strains generated from diploid and tetraploid species more than 1000 years ago. It has been shown that these strains confer immunogenicity and have a lower percentage of α, β, γ, and ω gliadins. *Psyllium* [70] is an alternative to gluten because it has a minimal effect on the smell and texture of wheat and good cooking properties [71]. Bread made with psyllium is appreciated by both patients with CD and healthy individuals for its texture and flavor. Another alternative is the use of genetic engineering, via RNA interference, to silence genes that encode immunogenic epitopes [72]. Recent studies evaluated the silencing of the HMW-G gene in a transgenic wheat strain (Bobwhite) and found that the content of wet gluten and the period of crop development were decreased. Gene silencing is an alternative to the production of gluten-free products [73]. Other studies have performed genetic modifications in wheat with the deletion of essential gliadin genes. The deletion of the α-gliadin locus on chromosome 6 in a hexaploid strain of wheat (*Triticum aestivum*) decreased the number of immunogenic epitopes recognized by T-cells, but did not significantly affect the cooking properties [74]. The deleted gliadin genes may need to be replaced with non-immunogenic gliadin or avenin genes to improve dough elasticity. The transgenic wheat strain E82 has been used in patients with non-celiac gluten sensitivity with undetectable immunogenic peptides in feces, and the good tolerability and high acceptance of the bread characteristics of this strain have been presented [75]; this method is pending evaluation in patients with CD to confirm these promising results.

b) PRETREATED FLOURS

Another therapeutic measure is the fermentation of wheat flour with different probiotics of the genus *Lactobacillus*. The rationale is that *Lactobacillus* contains peptidases that, when incorporated into the sourdough during fermentation, hydrolyze glutamine and proline-rich gluten peptides, including the highly immunogenic 33-mer gliadin peptide [76]. In a double-blind study of 17 patients with CD, the symptomatic response to two types of bread containing 2 g of gluten was analyzed: one bread was fermented with traditional yeast and the other with

Lactobacillus. Intestinal permeability in the patients with CD who consumed the bread fermented with the traditional yeast was increased, as evidenced by the increased excretion of the carbohydrates lactulose and L-rhamnose. In contrast, intestinal permeability in the patients who consumed the bread fermented with *Lactobacillus* was not significantly changed. The main limitation of the study was the period of fermentation (2 days), which was not sufficient to evaluate the possible inactivation of peptidases and draw definitive conclusions [77]. Similar approaches include gluten degradation by proteases during wheat fermentation [78]. Bread produced with protease-treated flours has a lower concentration of glutamine and gliadin, but is crumbly and presents an unpleasant flavor. Other studies incubated gliadin with anti-transglutaminase antibodies and lysine methyl-ester. Gliadin with modified lysine loses its affinity for HLA-DQ2, which causes less activation of T-cells in the intestine. The pretreatment of whole-wheat flour with lysine methyl-ester and transglutaminase derived from *Streptomyces mobaraensis* reduced the stimulatory effect of the flour on T-cells [79]. The use of anti-transglutaminase of microbial origin improved bread texture and volume. However, the use of microbial transglutaminase in food preparations is still controversial, and more studies are needed to develop non-immunogenic flours and validate their use in the production of bread and other baked goods with a good consistency and high nutritional value [80, 81].

~~c) DETOXIFICATION OF GLUTEN USING DIGESTIVE PROTEASES~~

~~The hydrolysis of gluten proteins is difficult due to the presence of high concentrations of proline and glutamine. These amino acids inhibit proteolysis by gastric and pancreatic enzymes and by endopeptidases and exopeptidases of the intestinal brush border [82]. The partial digestion of gluten peptides produces large oligopeptides, such as 33-mer and 26-mer, which have a high affinity for HLA-DQ2 or DQ8. These oligopeptides are innocuous in most people but are responsible for CD pathogenesis. Hence, a potential treatment for CD is the use of extrinsic enzymes to hydrolyze these oligopeptides to smaller sizes and decrease their recognition by the immune system. Propyl endopeptidases (PEPs) can hydrolyze peptide bonds between a carboxyl group and an internal proline residue that are not hydrolyzed by digestive enzymes [83, 84]. Therefore, the dietary administration of PEP concomitant with gluten is a possible therapeutic approach to complement the action of digestive proteases, hydrolyzing glutamine and proline-rich immunogenic oligopeptides and preventing their accumulation [85]. At present, several candidate fungal and microbial PEPs are available for the treatment of CD. The PEPs from the fungus *Aspergillus niger* efficiently digests gluten proteins in vitro [83, 86]. PEPs from the bacterial species *Flavobacterium meningosepticum*, *Sphingomonas capsulata*, and *Myxococcus xanthus* [87] are active at duodenal pH, moderately resistant to acidic pH, and maintain**

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

~~enzymatic activity in the small intestine of rats [88]. A randomized, double-blind, crossover study analyzed 20 asymptomatic patients with CD on a GFD. These patients received 5 g gluten for 14 days and were randomized to receive gluten along with PEP from *Flavobacterium meningosepticum* for another 14 days. After 14 days, the administration of gluten with PEP resulted in improved absorption of carbohydrates and fats [89].~~

~~The co-administration of two proteases acting on complementary amino acid residues, a PEP from *Sphingomonas capsulata* that recognizes proline residues and a cysteine protease from germinated barley seeds that recognizes glutamine residues, has been investigated as a means to maximize the effectiveness of dietary supplementation with PEP. The combined action of these proteases completely detoxified gluten [90]. This two-enzyme system was designated IMGX-003 (previously ALV003), and the efficacy of this synergistic system was superior to that of the isolated peptidases [91]. The safety, tolerability, and activity of IMGX-003 were assessed in two randomized, double-blind, controlled placebo-crossover, Phase 1 clinical trials using a single ascending dose (100, 300, 900, and 1800 mg) of ALV003 [92]. The first study included twenty-four healthy volunteers and four patients with CD; all patients were administered ALV003 in the fasted state. The second study comprised 52 healthy volunteers and one patient with CD who received the endopeptidase together with 1 g of gluten per day. All patients tolerated ALV003 without severe adverse effects. The second study found that 100 mg and 300 mg of ALV003 degraded gluten in the human stomach, similar to in vitro observations. A Phase IIa study provided either ALV003 or placebo to 20 patients with CD and randomized them to receive 16 g of gluten for 3 days. There were no significant differences in the clinical response between the two groups. Nonetheless, the participants in the intervention group did not present with intestinal mucosal lesions, whereas the placebo group experienced an increase in intraepithelial lymphocytes. A Phase IIa clinical trial was conducted to determine the efficacy and safety of ALV003 for the prevention of gastrointestinal symptoms caused by gluten and the improvement of the immune response of patients with CD. Adult patients with CD were randomized to receive either ALV003 (n = 20) or placebo (n = 21). Subsequently, 2 g gluten was administered daily for 2 months. There were no significant differences in symptoms between the two groups. The degree of histological damage in duodenal biopsies from patients with CD who received ALV003 was lower than that in the placebo group [93], suggesting that ALV003 could prevent histological damage in patients who consumed moderate doses of gluten. However, there are several limitations to oral enzyme therapy. First, the apparent lack of efficacy may be the greatest limitation to its use in conventional clinical practice. Second, it is necessary to determine the quantity of enzyme supplement that needs to be administered, the~~

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

~~ratio of endopeptidase administered relative to the amount of gluten ingested, and the length of therapy necessary to achieve the degradation of gluten-derived immunogenic peptides [85].~~

~~Other studies evaluated the efficacy of a PEP from *Aspergillus niger* (AN-PEP). A double-blind, randomized, controlled placebo-clinical trial examined the safety and efficacy of this PEP in sixteen patients with CD on a GFD with Marsh grade 0 duodenal histology [94]. In the first phase of the study, 7 g gluten was administered with AN-PEP for 2 weeks, and a duodenal biopsy was performed. The second phase involved the administration of a GFD without endopeptidases. In the third phase, fourteen patients without histological changes in the duodenal biopsy received 7 g gluten with either a placebo or AN-PEP for 2 weeks. No adverse effects were observed, and the scores on the quality of life questionnaires were highest of the three phases. The primary objective was to detect histological alterations. In the first phase, two patients presented with histological changes according to Marsh classification. In the third phase, in the placebo group, two patients presented as Marsh grade 2, and five patients had an increased number of intraepithelial lymphocytes. In the group treated with AN-PEP, only one patient exhibited worse histological scores, suggesting that AN-PEP was not effective in the prevention of mucosal damage induced by 7 g gluten per day. Nevertheless, it is necessary to assess whether AN-PEP is effective against lower doses of gluten or as a pretreatment before foods containing traces of gluten. Currently, the pharmacological process of AN-PEP has been interrupted and it is now available as a nutritional supplement.~~

~~Nevertheless, another second-line PEP currently in development is KumaMax. Although the actual development is phase I, this glutenase has a power 100 times higher than IMGX 003 [95].~~

5. INTRALUMINAL THERAPIES

a) DETOXIFICATION OF GLUTEN USING DIGESTIVE PROTEASES

The hydrolysis of gluten proteins is difficult due to the presence of high concentrations of proline and glutamine. These amino acids inhibit proteolysis by gastric and pancreatic enzymes and by endopeptidases and exopeptidases of the intestinal brush border [82]. The partial digestion of gluten peptides produces large oligopeptides, such as 33-mer and 26-mer, which have a high affinity for HLA-DQ2 or DQ8. These oligopeptides are innocuous in most people but are responsible for CD pathogenesis. Hence, a potential treatment for CD is the use of extrinsic enzymes to hydrolyze these oligopeptides to smaller sizes and decrease their recognition by the immune system. Prolyl endopeptidases (PEPs) can hydrolyze peptide bonds between a carboxyl group and an internal proline residue that are not hydrolyzed by digestive enzymes [83, 84]. Therefore, the dietary administration of PEP concomitant with gluten is a possible

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

therapeutic approach to complement the action of digestive proteases, hydrolyzing glutamine and proline-rich immunogenic oligopeptides and preventing their accumulation [85]. At present, several candidate fungal and microbial PEPs are available for the treatment of CD. The PEPs from the fungus *Aspergillus niger* efficiently digests gluten proteins in vitro [83, 86]. PEPs from the bacterial species *Flavobacterium meningosepticum*, *Sphingomonas capsulata*, and *Myxococcus xanthus* [87] are active at duodenal pH, moderately resistant to acidic pH, and maintain enzymatic activity in the small intestine of rats [88]. A randomized, double-blind, crossover study analyzed 20 asymptomatic patients with CD on a GFD. These patients received 5 g gluten for 14 days and were randomized to receive gluten along with PEP from *Flavobacterium meningosepticum* for another 14 days. After 14 days, the administration of gluten with PEP resulted in improved absorption of carbohydrates and fats [89].

The co-administration of two proteases acting on complementary amino acid residues, a PEP from *Sphingomonas capsulata* that recognizes proline residues and a cysteine protease from germinated barley seeds that recognizes glutamine residues, has been investigated as a means to maximize the effectiveness of dietary supplementation with PEP. The combined action of these proteases completely detoxified gluten [90]. This two-enzyme system was designated ALV003, ~~IMGX-003 (previously~~ IMGX-003,~~ALV003)~~ or latiglutenase, and the efficacy of this synergistic system was superior to that of the isolated peptidases [91]. The safety, tolerability, and activity of IMGX-003 were assessed in two randomized, double-blind, controlled-placebo crossover, Phase 1 clinical trials using a single ascending dose (100, 300, 900, and 1800 mg) of ALV003 [92]. The first study included twenty-four healthy volunteers and four patients with CD; all patients were administered ALV003 in the fasted state. The second study comprised 52 healthy volunteers and one patient with CD who received the endopeptidase together with 1 g of gluten per day. All patients tolerated ALV003 without severe adverse effects. The second study found that 100 mg and 300 mg of ALV003 degraded gluten in the human stomach, similar to in vitro observations[92]. A Phase IIa study provided either ALV003 or placebo to 20 patients with CD and randomized them to receive 16 g of gluten for 3 days[93]. There were no significant differences in the clinical response between the two groups. Nonetheless, the participants in the intervention group did not present with intestinal mucosal lesions, whereas the placebo group experienced an increase in intraepithelial lymphocytes. A Phase IIa clinical trial was conducted to determine the efficacy and safety of ALV003 for the prevention of gastrointestinal symptoms caused by gluten and the improvement of the immune response of patients with CD. Adult patients with CD were randomized to receive either ALV003 (n = 20) or placebo (n = 21)[94]. Subsequently, 2 g gluten was administered daily for 2 months. There were no significant

Código de campo cambiado
Código de campo cambiado
Código de campo cambiado
Código de campo cambiado
Código de campo cambiado
Código de campo cambiado

differences in symptoms between the two groups. The degree of histological damage in duodenal biopsies from patients with CD who received ALV003 was lower than that in the placebo group [94], suggesting that ALV003 could prevent histological damage in patients who consumed moderate doses of gluten. A subsequent, larger (n=494) phase II study examined the effects of oral ALV003 on mucosal morphometric abnormalities in biopsies from patients with nonresponsive CD despite following a GFD for at least 1 year[95]. Patients were assigned randomly to receive placebo or ALV003 (100–900 mg/d for 12 or 24 weeks).The primary end point was a change in the villous height/crypt depth ratio but there were no significant differences between ALV003 and placebo groups in this outcome measure. All groups, including placebo, had significant improvements both in histologic and in symptom scores, indicating a trial effect of more stringent dietary gluten avoidance. A post hoc subgroup analysis of the data from this study found a reduction in celiac related symptoms in Transglutaminase seropositive subjects that was most evident in those receiving the highest dose of ALV003 (900 mg). This finding opens the way for additional evaluation of ALV003 in selected patients at higher risk for continued gluten exposure. However, there are several limitations to oral enzyme therapy. First, the apparent lack of efficacy may be the greatest limitation to its use in conventional clinical practice. Second, it is necessary to determine the quantity of enzyme supplement that needs to be administered, the ratio of endopeptidase administered relative to the amount of gluten ingested, and the length of therapy necessary to achieve the degradation of gluten-derived immunogenic peptides [85]. Recently, a Phase III clinical trial randomized, double-blind, controlled-placebo with 398 patients following a GFD for at least one year was efectuated. Patients were treated for 12 weeks with ALV003 or placebo. The severity of abdominal pain and bloating was reduced by 58% and 44%, respectively, in the cohort receiving the highest ALV003 dose (900 mg, n=14) relative to placebo (n=54)[96]. A metaanalisis tries to explain this fact[97]. Celiac patients in GFD might unvoluntary take small quantities of gluten that can be metabolize by these enzymes decreasing the symptomatology.

Other studies evaluated the efficacy of a PEP from *Aspergillus niger* (AN-PEP). A double-blind, randomized, controlled-placebo clinical trial examined the safety and efficacy of this PEP in sixteen patients with CD on a GFD with Marsh grade 0 duodenal histology [98]. In the first phase of the study, 7 g gluten was administered with AN-PEP for 2 weeks, and a duodenal biopsy was performed. The second phase involved the administration of a GFD without endopeptidases. In the third phase, fourteen patients without histological changes in the duodenal biopsy received 7 g gluten with either a placebo or AN-PEP for 2 weeks. No adverse effects were observed, and the scores on the quality of life questionnaires were highest of the three phases. The primary

Código de campo cambiado

Código de campo cambiado

Código de campo cambiado

objective was to detect histological alterations. In the first phase, two patients presented with histological changes according to Marsh classification. In the third phase, in the placebo group, two patients presented as Marsh grade 2, and five patients had an increased number of intraepithelial lymphocytes. In the group treated with AN-PEP, only one patient exhibited worse histological scores, suggesting that AN-PEP was not effective in the prevention of mucosal damage induced by 7 g gluten per day. Nevertheless, it is necessary to assess whether AN-PEP is effective against lower doses of gluten or as a pretreatment before foods containing traces of gluten. Currently, the pharmacological process of AN-PEP has been interrupted and it is now available as a nutritional supplement.

Nevertheless, another second line PEP currently in development is KumaMax. Although the actual development is phase I, this glutenase has a power 100 times higher than IMGX-003[99].

Código de campo cambiado

b) GLUTEN-SEQUESTERING POLYMERS (BL-7010)

An alternative to gluten detoxification is the oral use of polymer resins such as poly-hydroxyethyl-methacrylate-co-styrene-sulfonate (P-HEMA-co-ss) or BL-7010 [100, 101], which sequester intraluminal gliadin and consequently prevent the access of immunogenic gluten peptides to the intestinal mucosa. In vitro studies, in murines, have shown that this polymer agglutinates gliadin molecules and prevents their degradation. In vivo studies in transgenic HLA-DQ8 mice sensitized to gliadin demonstrated that the use of P-HEMA-co-ss decreased intestinal damage-[102]. However, it is necessary to determine whether this quench is specific to gliadin or if it may also block the availability of other nutrients. Indeed, it also remains to be confirmed whether gluten can be also effectively neutralized by this resin in vivo. In Phase I studies of this compound, the most common side effect was diarrhea.

c) GLUTEN-NEUTRALIZING ANTIBODIES

Potential problems related to the non-specificity of polymers are minimized if specific oral IgG antibodies that bind to and inactivate intraluminal antigens are used, as observed in other diseases, such as *Clostridium difficile* infection [103, 104]. Cow colostrum has been used because it is readily available and contains a high concentration of antibodies. Nonetheless, the lack of clinical efficacy of this type of antibody prevented its analysis in Phase I studies. The use of antibodies that neutralize the IgY gluten from hen's egg yolk has been proposed as a safe and effective therapy for patients with CD with mild or moderate symptoms due to short-term non-compliance with a GFD and who are not allergic to eggs [105]. Ten patients with mild to moderate symptoms received 1 g of antibodies daily during meals. This treatment had a good safety profile; the quality of life and associated symptoms improved, IgA anti-transglutaminase

antibody titer decreased, and the intestinal permeability to lactulose and mannitol was improved at 6 weeks [106]. These antibodies may be labeled as food additives and can be used as an adjuvant therapy that would not render the strict compliance with GFD unnecessary, but would allow short-term non-compliance (e.g., during trips, meetings, and social events) and improve the quality of life for patients.

~~5.~~6. IMMUNOMODULATION AND GLUTEN TOLERANCE

a) HELMINTH THERAPY

Given that CD is triggered by the lack of immune tolerance to dietary antigens, corroborating the precepts of the hygiene hypothesis [107], several approaches have been used to modulate the immune system and desensitize its response to gluten. One of the strategies used to control the immunoregulatory activity is helminth therapy, predominantly with the pig roundworm *Trichuris suis* and the human hookworm *Necator americanus*, with variable success [108, 109]. Chronic infection with helminths, such as hookworms, has been proposed to alter the Th1 immune response, allowing the control of different inflammatory pathologies, including inflammatory bowel disease (IBD) and CD. However, the use of hookworms in Crohn's disease did not control the symptoms, limiting therefore its therapeutic usefulness [110]; notwithstanding, this strategy may be useful for the treatment of CD. In a double-blind, placebo-controlled study conducted for 21 weeks, patients with CD on a GFD were infected with *Necator americanus* and subsequently received a gluten-containing diet. Although there were no significant differences in clinical manifestations between both groups, patients with hookworm infections had less intestinal mucosal inflammation, decreased levels of IFN-γ, IL-17, IL-23, and higher levels of IL-10 and TGF-β [109]. Another study conducted for 52 weeks in 12 patients infected with *Necator americanus* after the controlled and gradual introduction of gluten in the diet reported the absence of histological lesions in the intestine and lower anti-transglutaminase antibody titers over time [111]. These findings suggested that long-term helminth infection in the intestine suppresses the immune response to gluten and does not cause severe side effects. Nevertheless, more studies are needed to confirm these findings and the safety of the treatment.

b) INDUCTION OF MUCOSAL TOLERANCE

An alternative approach to desensitize the immune response to gluten is the direct induction of immune tolerance in the intestinal mucosa [112]. Using murine models (HLA-Q8^{+}) of CD, the peripheral immunization of the intestinal mucosa with α-gliadin via the intranasal route decreased IFN-γ levels and the proliferation of T lymphocytes, and increased the levels of IL-10

[113, 114]. Gliadin previously treated with *Lactococcus lactis* was administered together with a biodegradable polymer (TIMP) composed of lactic-co-glycolic-acid with gliadin in its nucleus (TIMP-GLI), allowing the compound to reach the lymphoid tissues, where the APCs are located. However, it was not possible to determine whether this strategy could suppress the immune response of T-cells to other gluten epitopes. Currently, the safety and pharmacokinetic profiles of intravenous TIMP-GLI in patients is under assessment in a Phase I trial (NCT03486990). In this trial 0,1- 0,5-1-2-4 y 8mg/kg de TIMP-GLI are administrated intravenously and it is evaluated in 48 hours its side effects, electrocardiogram, proinflammatory cytokine in blood and in urine determination in order to ensurance the safety of the product.

c) VACCINATION: NEXVAX2

The objective of immunotherapy is the induccion ~~complete recovery~~ of immune gluten tolerance ~~to gluten~~, which therefore renders this approach attractive to both patients and researchers. The efficacy of vaccines against allergic diseases for which antigenic peptides are known has already been demonstrated. The characterization of the gluten epitope repertoire enable the development of the drug nexvax2, which induces antigen-specific regulatory T-cell populations that decrease the pro-inflammatory activity mediated by classical T lymphocytes [115]. This vaccine is administered subcutaneously and contains three peptides derived from α-gliadin, ω-gliadin, and hornein, which collectively cover around 60% of the total immunogenic epitopes found in the gluten. Using murine models, such approach decreased T-cell proliferation together with the levels of IL-2 and IFN-γ by increasing the levels of regulatory T-cells [116]. The vaccine was evaluated in two multicenter, double-blind phase I studies with a hundred and eight and twenty-eight patients with CD following a GFD, respectively, who were randomized to receive nexvax2 at different doses (60 µg, 90 µg, 150 µg, and higher doses according to the patient's tolerance) or placebo. Different routes and times of administration were analyzed, being the primary objective the evaluation of side effects. Gastrointestinal symptoms, including nausea, vomiting, abdominal distention, or abdominal pain, occurred in 50% of patients between 2 and 5 hours of the administration of the first dose. However, these adverse effects were less frequent in subsequent doses, which indicated a specific immune tolerance to nexvax2. None of the evaluated patients presented a positive titer for anti-transglutaminase antibodies or anti-deamidated gliadin during treatment. Patients who received 150–300 µg underwent a duodenal biopsy between 15 and 28 days after the beginning of the study, and no changes in intestinal histology or lymphocyte number were observed [117]. These results evidenced that the intradermal administration of 150 µg of nexvax2 twice per week for 8 weeks could modulate the immune response to these immunogenic peptides without causing duodenal damage.

Although Goel et al. [117] analyzed the safety of this therapeutic approach, new experimental designs are necessary to fully confirm its efficacy. Indeed, it is important to note that it is needed to determine the amount of gluten that can be consumed by patients vaccinated with nexvax2, together with the duration of its protective effect. Also, a major limitation of vaccination is that it is only suitable for patients who harbor the HLA-DQ2.5 haplotype; as the peptides used for sensitization are only recognized by heterodimers [118]. This therefore renders at least one-third of the patients without the possibility of benefiting from this therapeutic approach. Hence, it is necessary to identify the specific epitopes that are recognized by all patients and that allow the safe reintroduction of gluten in the diet [54], regardless of the HLA haplotype.

~~6.~~7. MODULATION OF INTESTINAL PERMEABILITY

a) MODULATION OF THE TIGHT JUNCTIONS BETWEEN ENTEROCYTES: ZONULIN RECEPTOR ANTAGONISTS

In healthy individuals, the tight junctions between intestinal epithelial cells control the movement of substances from the lumen of the gastrointestinal tract to the circulation. Tight junctions are impaired in patients with CD and in their first-degree relatives, causing an increased intestinal permeability, which ultimately increases the transfer of gluten peptides to the lamina propria, where they can trigger immune responses [119, 120]. Zonulin is a precursor of prehaptoglobin-2, which regulates epithelial permeability and is overexpressed in the intestine of patients with CD compared with healthy subjects [121]. The effect of zonulin is similar to that of the zonula occludens toxin (ZOT), which is secreted by *Vibrio cholerae*. Zonulin decreases intestinal permeability through the disruption of the tight junctions [121]. Lammers et al. [122] shown that gliadin binds to the CXCR3 receptor and triggers the synthesis of zonulin, which enhances an increase in intestinal permeability. Larazotide acetate or INN-201 (previously known as AT1001), an octapeptide derived from ZOT, antagonizes the action of zonulin by blocking the CXCR3 receptor and preventing therefore the intestinal damage mediated by ZOT [123]. A randomized, double-blind Phase 1 clinical trial evaluated the safety and efficacy of this orally administered drug: gluten associated with AT1001 was administered to fourteen patients with CD for 4 days consecutively, being these patients compared with a group of seven patients who received placebo (without gluten) [124]. Intestinal permeability in both groups was determined through the measurement of the excretion of lactulose and mannitol. Upon stimulation with gluten, intestinal permeability remained intact in the intervention group, and the number of adverse events, gastrointestinal symptoms, and inflammatory markers were not increased in this group compared with the placebo group. A Phase IIb study evaluated a hundred and eighty-four patients with CD in remission, in which the patients received ascending doses of

AT1001 followed by 3 g gluten daily for 42 days. Although sixty-one patients showed significant improvement in gastrointestinal symptoms and a lower serological titer, the primary objective of the study (to assess improvements in intestinal permeability by the decreased levels of lactulose and mannitol in the feces) was not achieved [125]. Other Phase IIb studies determined the efficacy of different doses of larazotide [126, 127, 128]. A preliminary trial (CLIN1001-004) [127] evaluated different doses of AT1001 (0.25, 1, 4, and 8 mg three times per day) in eighty-six patients with CD in remission following a GFD for 6 months. Patients were randomized to receive either larazotide or placebo. The excretion of lactulose and mannitol was lower in the patients treated with 1 mg of the drug, but the intergroup differences were not statistically significant. Moreover, these patients exhibited better clinical response and an IgA anti-transglutaminase antibody titer of less than 10 IU/mL. In a second trial (CLIN 1001-006) [126], a hundred and eighty-six patients with CD following a GFD for 6 months were randomized to receive either larazotide (1, 4, or 8 mg three times per day) or placebo. The excretion of lactulose and mannitol and clinical symptoms were lower in the group that received 1 mg AT1001, although this difference was not statistically significant. Furthermore, the largest study conducted on this subject (CLIN 1001-012) analyzed the efficacy of larazotide in three hundred and forty-two patients with CD following a GFD for more than 1 year with persistent symptoms [128]. This study did not use high doses of gluten, and the participants were randomized to receive either larazotide (0.5, 1, or 2 mg three times per day) or placebo. The treatment with 0.5 mg significantly reduced digestive and extra-digestive symptoms (especially headache and asthenia) compared with placebo, demonstrating an inverse relationship between the therapeutic effect and the administered dose; i.e., lower doses were more effective than higher doses. The possible explanations for this dose-response relationship are the desensitization of the receptor or the aggregation of the peptide at higher doses leading to a lower therapeutic effect. Therefore, larazotide may be a novel treatment for managing the symptoms of patients with CD on a GFD and improving their quality of life [125].

~~7.~~8. MODULATION OF THE ADAPTIVE IMMUNE RESPONSE

a) TRANSGLUTAMINASE INHIBITORS

Tissue transglutaminase type 2 (TG2) is an intracellular enzyme that plays a fundamental role in the pathogenesis of CD. Gluten-derived peptides are presented to T-cells by APCs via HLA-DQ2 or HLA-DQ8 molecules. However, gliadin peptides need to be deaminated by TG2 to be properly accommodated in the HLA-DQ2/8 bound, which allows a more efficient antigenic presentation and, therefore, the trigger of an adaptive immune response. The inhibition of gliadin deamination by TG2 inhibitors reduces the binding affinity of the peptides to APCs [51]. TG2

inhibitors are classified by their mechanism of action as competitive cinnamoyl triazole, reversible, or irreversible. Competitive cinnamoyl triazole inhibitors inhibit the activity of TG2, competing and blocking the access of the substrate to the active site without covalent modification of the enzyme. In contrast, irreversible TG2 inhibitors bind irreversibly to the enzyme, causing covalent modification. Rauhavirta et al. [129] demonstrated that the direct toxic effects of predigested gliadin (trans-epithelial resistance, cytoskeletal reorganization, expression of binding proteins, and phosphorylation of the extracellular-signal regulated kinase) in intestinal cultures were reduced in the presence of two irreversible TG2 inhibitors (R281 and R283). In addition, the authors measured the secretion of TG2 autoantibodies in cultures of mucosal biopsies of the small intestine from patients with CD and quantified the levels of regulatory T-cells and Ki-67-positive crypt cells following exposure to gluten. R281 increased the number of CD25-positive cells, regulatory T-cells, and the proliferation of crypt cells, but did not significantly affect the secretion of antibodies in biopsies of patients with CD. Although these results are promising, TG2 is a ubiquitous enzyme and its sequence is similar to that of other types of transglutaminases, non-selective inhibitors may present systemic side effects. This limitation was overcome through the development of three soluble transglutaminase inhibitors (ZED1098, ZED1219, and ZED1227) highly selective to intestinal TG2, which increased their therapeutic utility in CD. However, TG2 deficiency in murine models has been associated with splenomegaly, the production of autoantibodies, and the development of glomerulonephritis [130], suggesting the importance of caution in the development of therapeutic approaches focused on inhibition of TG2. Actuality, phase 2 trials on tgase-inhibitor ZED1227 are currently recruiting patients. (EudraCT Number: 2017-002241-30)

b) HLA-DQ2 BLOCKERS

The blockade of HLA-DQ2 or DQ8 molecules is a promising therapeutic strategy to prevent the activation of gluten by the immune system. This therapy has been previously evaluated in other diseases associated with the HLA system although it has been ineffective. This is likely due to the difficulty of specifically targeting the drugs to the affected tissues. Nevertheless, drugs can reach the intestinal epithelium of patients with CD via the oral route [131]. In this regard, several peptides with a high affinity for HLA-DQ2 have been designed by amino acid substitution and dimerization or inclusion of the aldehyde groups [20]. These peptide antagonists have shown moderate efficacy in the inhibition of the production of IFN-γ in cell cultures of patients with CD,

demonstrating a potential to decrease the gluten-induced activation of T-cells. The main drawback of HLA blockers is the ability to maintain partial agonist effects on gliadin-stimulated T-cells, which causes an exacerbated immune response. In addition, the binding affinity of most antagonist peptides is not strong enough to completely block the access of stimulatory gliadin peptides to HLA-DQ2. Consequently, efforts have been intensified to identify optimal HLA-DQ2 antagonists, particularly those based on peptides, with 50 times higher binding affinity to HLA-DQ2 than the immunodominant gluten peptides. Nonetheless, it is unknown whether this type of HLA-DQ2 blocker can reach its target in the lamina propria or compete with gluten-derived peptides, and whether these blockers cause hypersensitivity reactions or immunosuppression that lead to secondary infections. At present, preclinical studies on the inhibition of HLA-DQ2 are under development to identify and evaluate the efficacy of a non-toxic, non-immunogenic, and highly specific antagonist with a high affinity for HLA DQ2.

~~8.~~9. OTHER EXPERIMENTAL TREATMENTS

Although the described alternative strategies to GFD in patients with CD are specific for this disease, it should be stressed that CD is immune-mediated. Therefore, it is not surprising that the inflammatory processes occurring in these patients share mechanistic and functional similarities with other inflammatory diseases of the gastrointestinal tract, including IBD. Most of the current research in new drugs for intestinal inflammation focuses on IBD; however, in contrast to CD, in which it is possible to control the immune response via the GFD, some of the drugs designed to desensitize the immune response in patients with IBD may be effective in CD.

These drugs include the humanized monoclonal antibody specifically directed against integrin $\alpha4\beta7$ (vedolizumab), which inhibits leukocyte migration and adhesion to the gastrointestinal tract and may therefore be an effective treatment for CD. In this respect, a clinical trial (NCT02929316) to evaluate the benefit of blocking the leukocyte migration and adhesion to the intestinal mucosa is currently underway. Other drugs that block leukocyte migration to the gastrointestinal tract include CCR9 receptor inhibitors that, in contrast to integrin $\alpha4\beta7$, which inhibits cellular migration to the entire gastrointestinal tract, specifically block immune migration to the small intestine, the side of inflammation in CD [132].

~~The inhibition of the CD40-CD40L interaction, anti-IFN-γ and anti-TNF-α therapies, JAK-Stat inhibitors, and IL-10 and -IL-22 agonists are potential therapeutic options that were tested for IBD and which are under evaluation for RCD. Similarly, given the essential role of IL-15 in the pathogenesis of celiac disease, its neutralization is being explored in CD and RCD II given that the proliferation of premalignant and malignant lymphocytes depends on IL-15. A Phase II~~

~~clinical trial evaluated the efficacy of the anti-IL-15 monoclonal antibody AMG714 in patients with rheumatoid arthritis and psoriasis, finding that the treatment was effective for rheumatoid arthritis [82]. Phase IIa clinical trials of AMG 714 for CD (NCT02637141) and RCD II (NCT02633020) were concluded; the preliminary results were presented during the 2018 DDW meeting. In both studies, the effect of IL-15 versus placebo was determined over 12 weeks in CD and 2 weeks in RCD II. The monoclonal antibody AMG714, named as PRV-015, showed an excellent tolerance with a significant decrease of symptoms and duodenal lymphocyte infiltrate in CD patients. In those with RCD II, AMG 714 successfully blocked the pathogenic process, as it prevented T-cell clonal expansion. Phase IIb trials has been announced to demonstrate the efficacy of IL-15 antagonist in CD with failure to GFD response and RCD.~~

~~Cladribine (2-CdA) is a synthetic purine nucleoside with a cytotoxic effect and represents a promising therapy for RCD II. In addition, recent studies assessed the effectiveness of allogeneic bone marrow transplantation for the treatment of ECR II or EATL because of its high therapeutic potential, despite the possibility of several immunological complications. Furthermore, therapeutics with mesenchymal stem cells may be a useful option because of their low immunogenic potential and the absence of co-stimulatory molecules. Therefore, this therapeutic modality has potential applications in the treatment of RCD II and EATL; however, no clinical trials to date have evaluated its efficacy.~~

~~9.~~10. EXPERT OPINION

Strict compliance to the GFD is currently the only effective therapy for CD. Although patients with type I or type II RCD present a premalignant profile and therefore require active immunomodulation to reduce disease development, the restoration of intestinal homeostasis can be quickly and easily achieved in most patients with classical CD by strict compliance with a GFD. Moreover, in most cases, a GFD is more cost-effective than active interventions with drug therapies. Therefore, the pharmacological treatment of CD requires a cost-benefit ratio similar to that of GFDs. Nevertheless, the restriction of gluten consumption is difficult for some patients, especially those who are diagnosed as an adult and must make lifestyle changes. Moreover, compliance is challenging because of economic reasons (higher cost of gluten-free products), technical reasons (purchase of food products with proven safety and no possibility of cross-contamination), and social reasons (incompatibility of diet with lifestyle). In addition, despite adherence to a GFD, some patients have symptoms and/or histological lesions even in the absence of RCD. Although it is true that a GFD is the preferred approach for all patients, it should not be forgotten that GFD can be entirely or partially complemented with other therapies. Three

potential alternative or complementary strategies to GFDs can be adopted, depending on whether one seeks a better quality of gluten-free foods, a specific immunomodulation strategy, or a complete intervention.

The more significant limitations of GFDs are that gluten-free products are more expensive and their organoleptic properties may be different from those of traditional gluten-containing products. Therefore, the modification of dietary gluten (described in Section 4a) would allow the development of better and/or cheaper gluten-free products. This strategy would not therefore eliminate the need for GFD, but could make it more attractive for patients, thereby increasing the rate of adherence to treatment.

The therapies discussed in Sections 4b, 5, 7, 8, and 9 are based on immunomodulation. In these cases, the long-term adoption of different strategies is needed to suppress the active immune response to gluten. These therapies are therefore less cost-effective than full compliance to the GFD, but may be beneficial when used in a timely manner. This would be the case for instance of newly diagnosed patients where complementary to the GFD, immunomodulation would improve the clinical and mucosal recovery in the short-term. Furthermore, the patients who achieve clinical and histological remission may benefit from the withdrawal of the medication and remain exclusively on a GFD, although they may be treated appropriately in situations in which dietary compliance is beyond their control (e.g., leisure and travel).

Last, but not least, the strategies detailed in Section 6 aim to induce oral tolerance to dietary antigens. In contrast to prophylactic measures, these approaches would be curative and permanently eliminate the need for dietary compliance. This option is the most desired by patients, but has the most difficulties and restrictions, as previously discussed.

Notwithstanding, progress has been made in recent years in the development of new therapeutics for CD, as evidenced by the different approaches described in this review. Therefore, it is expected that shortly, alternative or complementary tools for the treatment of GFD will be available to patients with CD and will improve their quality of life.

Funding:

This study was funded in part by a grant from the Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (Ref PI13/01133 and PI16/01574), cofunded by FEDER (European Regional Development Fund).

Declaration of Interest:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

References

1. Murray JA, Frey MR, Oliva-Hemker M. Celiac Disease. Gastroenterology. 2018;154(8):2005-8. Epub 2018/03/20.
2. Ludvigsson JF, Rubio-Tapia A, van Dyke CT, Melton LJ, 3rd, Zinsmeister AR, Lahr BD, et al. Increasing incidence of celiac disease in a North American population. The American journal of gastroenterology. 2013;108(5):818-24. Epub 2013/03/21.
3. Rodrigo L, Garrote JA, Vivas S. [Celiac disease]. Medicina clinica. 2008;131(7):264-70. Epub 2008/09/09. Enfermedad celiaca.
4. Robert ME, Crowe SE, Burgart L, Yantiss RK, Lebwohl B, Greenson JK, et al. Statement on Best Practices in the Use of Pathology as a Diagnostic Tool for Celiac Disease: A Guide for

Clinicians and Pathologists. The American journal of surgical pathology. 2018;42(9):e44-e58. Epub 2018/06/21.
5. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology. 2006;131(6):1981-2002. Epub 2006/11/08.
6. Vaquero L, Caminero A, Nunez A, Hernando M, Iglesias C, Casqueiro J, et al. Coeliac disease screening in first-degree relatives on the basis of biopsy and genetic risk. European journal of gastroenterology & hepatology. 2014;26(3):263-7. Epub 2013/12/05.
7. Vaquero L, Rodriguez-Martin L, Alvarez-Cuenllas B, Hernando M, Iglesias-Blazquez C, Menendez-Arias C, et al. Coeliac Disease and Gastrointestinal Symptom Screening in Adult First-degree Relatives. Journal of gastroenterology and hepatology. 2017. Epub 2017/04/08.
8. Vaquero L, Rodriguez-Martin L, Hernando M, Jimenez M, Monteserin L, Alvarez-Cuenllas B, et al. Duodenal mucosa FOXP3 expression in different etiologies of lymphocytic duodenosis. Histology and histopathology. 2017:11888. Epub 2017/03/11.
9. Vaquero L, Alvarez-Cuenllas B, Rodriguez-Martin L, Aparicio M, Jorquera F, Olcoz JL, et al. [A review of diseases related to the intake of gluten]. Nutricion hospitalaria. 2015;31(6):2359-71. Epub 2015/06/05. Revision de las patologias relacionadas con la ingesta de gluten.
10. Rubio-Tapia A, Rahim MW, See JA, Lahr BD, Wu TT, Murray JA. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. The American journal of gastroenterology. 2010;105(6):1412-20. Epub 2010/02/11.
11. Lebwohl B, Granath F, Ekbom A, Montgomery SM, Murray JA, Rubio-Tapia A, et al. Mucosal healing and mortality in coeliac disease. Alimentary pharmacology & therapeutics. 2013;37(3):332-9. Epub 2012/11/30.
12. Theethira TG, Dennis M, Leffler DA. Nutritional consequences of celiac disease and the gluten-free diet. Expert review of gastroenterology & hepatology. 2014;8(2):123-9. Epub 2014/01/15.
13. Theethira TG, Dennis M. Celiac disease and the gluten-free diet: consequences and recommendations for improvement. Dig Dis. 2015;33(2):175-82. Epub 2015/05/01.
14. Lanzini A, Lanzarotto F, Villanacci V, Mora A, Bertolazzi S, Turini D, et al. Complete recovery of intestinal mucosa occurs very rarely in adult coeliac patients despite adherence to gluten-free diet. Alimentary pharmacology & therapeutics. 2009;29(12):1299-308. Epub 2009/03/24.
15. Barratt SM, Leeds JS, Sanders DS. Quality of life in Coeliac Disease is determined by perceived degree of difficulty adhering to a gluten-free diet, not the level of dietary adherence ultimately achieved. Journal of gastrointestinal and liver diseases : JGLD. 2011;20(3):241-5. Epub 2011/10/01.
16. Vaquero L, Alvarado MG, Arias L, Calleja S, Hernando M, Diez-Tascon C, et al. [Enteropathy associated intestinal t cell lymphoma without celiac disease]. Gastroenterologia y hepatologia. 2012;35(1):17-21. Epub 2011/12/20. Linfoma intestinal de celulas T asociado a enteropatia y sin relacion con enfermedad celiaca.
17. Vivas S, Ruiz de Morales JM, Ramos F, Suarez-Vilela D. Alemtuzumab for refractory celiac disease in a patient at risk for enteropathy-associated T-cell lymphoma. The New England journal of medicine. 2006;354(23):2514-5. Epub 2006/06/09.
18. Comino I, Moreno Mde L, Sousa C. Role of oats in celiac disease. World journal of gastroenterology. 2015;21(41):11825-31. Epub 2015/11/12.
19. Comino I, Real A, de Lorenzo L, Cornell H, Lopez-Casado MA, Barro F, et al. Diversity in oat potential immunogenicity: basis for the selection of oat varieties with no toxicity in coeliac disease. Gut. 2011;60(7):915-22. Epub 2011/02/15.
20. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies. Gastroenterology. 2009;137(6):1912-33. Epub 2009/09/22.

21. Maiuri L, Ciacci C, Ricciardelli I, Vacca L, Raia V, Auricchio S, et al. Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. Lancet. 2003;362(9377):30-7. Epub 2003/07/11.
22. Di Sabatino A, Giuffrida P, Fornasa G, Salvatore C, Vanoli A, Naviglio S, et al. Innate and adaptive immunity in self-reported nonceliac gluten sensitivity versus celiac disease. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2016;48(7):745-52. Epub 2016/05/01.
23. Montalvillo E, Bernardo D, Martinez-Abad B, Allegretti Y, Fernandez-Salazar L, Calvo C, et al. Increased Intraepithelial Valpha24 Invariant NKT Cells in the Celiac Duodenum. Nutrients. 2015;7(11):8960-76. Epub 2015/11/04.
24. Beckett CG, Dell'Olio D, Shidrawi RG, Rosen-Bronson S, Ciclitira PJ. Gluten-induced nitric oxide and pro-inflammatory cytokine release by cultured coeliac small intestinal biopsies. European journal of gastroenterology & hepatology. 1999;11(5):529-35. Epub 2001/02/07.
25. Murray IA, Daniels I, Coupland K, Smith JA, Long RG. Increased activity and expression of iNOS in human duodenal enterocytes from patients with celiac disease. American journal of physiology Gastrointestinal and liver physiology. 2002;283(2):G319-26. Epub 2002/07/18.
26. Daniels I, Cavill D, Murray IA, Long RG. Elevated expression of iNOS mRNA and protein in coeliac disease. Clinica chimica acta; international journal of clinical chemistry. 2005;356(1-2):134-42. Epub 2005/06/07.
27. De Stefano D, Maiuri MC, Iovine B, Ialenti A, Bevilacqua MA, Carnuccio R. The role of NF-kappaB, IRF-1, and STAT-1alpha transcription factors in the iNOS gene induction by gliadin and IFN-gamma in RAW 264.7 macrophages. J Mol Med (Berl). 2006;84(1):65-74. Epub 2005/11/15.
28. Martin-Pagola A, Perez-Nanclares G, Ortiz L, Vitoria JC, Hualde I, Zaballa R, et al. MICA response to gliadin in intestinal mucosa from celiac patients. Immunogenetics. 2004;56(8):549-54. Epub 2004/10/19.
29. Clemente MG, De Virgiliis S, Kang JS, Macatagney R, Musu MP, Di Pierro MR, et al. Early effects of gliadin on enterocyte intracellular signalling involved in intestinal barrier function. Gut. 2003;52(2):218-23. Epub 2003/01/14.
30. Sander GR, Cummins AG, Henshall T, Powell BC. Rapid disruption of intestinal barrier function by gliadin involves altered expression of apical junctional proteins. FEBS letters. 2005;579(21):4851-5. Epub 2005/08/16.
31. Barone MV, Zanzi D, Maglio M, Nanayakkara M, Santagata S, Lania G, et al. Gliadin-mediated proliferation and innate immune activation in celiac disease are due to alterations in vesicular trafficking. PloS one. 2011;6(2):e17039. Epub 2011/03/03.
32. Di Sabatino A, Ciccocioppo R, Cupelli F, Cinque B, Millimaggi D, Clarkson MM, et al. Epithelium derived interleukin 15 regulates intraepithelial lymphocyte Th1 cytokine production, cytotoxicity, and survival in coeliac disease. Gut. 2006;55(4):469-77. Epub 2005/08/18.
33. Meresse B, Chen Z, Ciszewski C, Tretiakova M, Bhagat G, Krausz TN, et al. Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease. Immunity. 2004;21(3):357-66. Epub 2004/09/11.
34. Hue S, Mention JJ, Monteiro RC, Zhang S, Cellier C, Schmitz J, et al. A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. Immunity. 2004;21(3):367-77. Epub 2004/09/11.
35. Escudero-Hernandez C, Pena AS, Bernardo D. Immunogenetic Pathogenesis of Celiac Disease and Non-celiac Gluten Sensitivity. Current gastroenterology reports. 2016;18(7):36. Epub 2016/05/25.
36. Raki M, Tollefsen S, Molberg O, Lundin KE, Sollid LM, Jahnsen FL. A unique dendritic cell subset accumulates in the celiac lesion and efficiently activates gluten-reactive T cells. Gastroenterology. 2006;131(2):428-38. Epub 2006/08/08.
37. Yoshimura S, Bondeson J, Brennan FM, Foxwell BM, Feldmann M. Role of NFkappaB in antigen-presentation and development of regulatory T cells elucidated by treatment of dendritic

cells with the proteasome inhibitor PSI. European journal of immunology. 2001;31(6):1883-93. Epub 2001/07/04.
38. Ouaaz F, Arron J, Zheng Y, Choi Y, Beg AA. Dendritic cell development and survival require distinct NF-kappaB subunits. Immunity. 2002;16(2):257-70. Epub 2002/03/01.
39. Ohteki T, Tada H, Ishida K, Sato T, Maki C, Yamada T, et al. Essential roles of DC-derived IL-15 as a mediator of inflammatory responses in vivo. The Journal of experimental medicine. 2006;203(10):2329-38. Epub 2006/09/13.
40. Pabst O, Mowat AM. Oral tolerance to food protein. Mucosal immunology. 2012;5(3):232-9. Epub 2012/02/10.
41. Mowat AM. Anatomical basis of tolerance and immunity to intestinal antigens. Nature reviews Immunology. 2003;3(4):331-41. Epub 2003/04/02.
42. Karell K, Louka AS, Moodie SJ, Ascher H, Clot F, Greco L, et al. HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. Human immunology. 2003;64(4):469-77. Epub 2003/03/26.
43. Anderson RP, Degano P, Godkin AJ, Jewell DP, Hill AV. In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope. Nature medicine. 2000;6(3):337-42. Epub 2000/03/04.
44. Arentz-Hansen H, McAdam SN, Molberg O, Fleckenstein B, Lundin KE, Jorgensen TJ, et al. Celiac lesion T cells recognize epitopes that cluster in regions of gliadins rich in proline residues. Gastroenterology. 2002;123(3):803-9. Epub 2002/08/29.
45. Nilsen EM, Jahnsen FL, Lundin KE, Johansen FE, Fausa O, Sollid LM, et al. Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. Gastroenterology. 1998;115(3):551-63. Epub 1998/08/28.
46. Leon AJ, Garrote JA, Blanco-Quiros A, Calvo C, Fernandez-Salazar L, Del Villar A, et al. Interleukin 18 maintains a long-standing inflammation in coeliac disease patients. Clinical and experimental immunology. 2006;146(3):479-85. Epub 2006/11/15.
47. MacDonald TT, Bajaj Elliott M, Pender SL. T cells orchestrate intestinal mucosal shape and integrity. Immunology today. 1999;20(11):505-10. Epub 1999/10/26.
48. Jabri B, Kasarda DD, Green PH. Innate and adaptive immunity: the yin and yang of celiac disease. Immunological reviews. 2005;206:219-31. Epub 2005/07/29.
49. Jabri B, Sollid LM. Mechanisms of disease: immunopathogenesis of celiac disease. Nature clinical practice Gastroenterology & hepatology. 2006;3(9):516-25. Epub 2006/09/05.
50. Londei M, Ciacci C, Ricciardelli I, Vacca L, Quaratino S, Maiuri L. Gliadin as a stimulator of innate responses in celiac disease. Molecular immunology. 2005;42(8):913-8. Epub 2005/04/15.
51. Gianfrani C, Auricchio S, Troncone R. Adaptive and innate immune responses in celiac disease. Immunology letters. 2005;99(2):141-5. Epub 2005/05/07.
52. Koning F. Celiac disease: caught between a rock and a hard place. Gastroenterology. 2005;129(4):1294-301. Epub 2005/10/19.
53. Koning F, Gilissen L, Wijmenga C. Gluten: a two-edged sword. Immunopathogenesis of celiac disease. Springer seminars in immunopathology. 2005;27(2):217-32. Epub 2005/08/11.
54. Tye-Din JA, Galipeau HJ, Agardh D. Celiac Disease: A Review of Current Concepts in Pathogenesis, Prevention, and Novel Therapies. Frontiers in pediatrics. 2018;6:350. Epub 2018/12/07.
55. Halmos EP, Clarke D, Pizzey C, Tye-Din JA. Gluten in "gluten-free" manufactured foods in Australia: a cross-sectional study. The Medical journal of Australia. 2018;209(10):448-9. Epub 2018/11/09.
56. C D, Berry N, Vaiphei K, Dhaka N, Sinha SK, Kochhar R. Quality of life in celiac disease and the effect of gluten-free diet. JGH open : an open access journal of gastroenterology and hepatology. 2018;2(4):124-8. Epub 2018/11/30.

57. Reilly NR, Lebwohl B, Hultcrantz R, Green PH, Ludvigsson JF. Increased risk of non-alcoholic fatty liver disease after diagnosis of celiac disease. Journal of hepatology. 2015;62(6):1405-11. Epub 2015/01/27.
58. Lebwohl B, Cao Y, Zong G, Hu FB, Green PHR, Neugut AI, et al. Long term gluten consumption in adults without celiac disease and risk of coronary heart disease: prospective cohort study. BMJ. 2017;357:j1892. Epub 2017/05/04.
59. Rashtak S, Murray JA. Review article: coeliac disease, new approaches to therapy. Alimentary pharmacology & therapeutics. 2012;35(7):768-81. Epub 2012/02/14.
60. Akobeng AK, Thomas AG. Systematic review: tolerable amount of gluten for people with coeliac disease. Alimentary pharmacology & therapeutics. 2008;27(11):1044-52. Epub 2008/03/05.
61. Schiepatti A, Bellani V, Perlato M, Maimaris S, Klersy C, Biagi F. Inadvertent and minimal gluten intake has a negligible role in the onset of symptoms in patients with coeliac disease on a gluten-free diet. The British journal of nutrition. 2018:1-23. Epub 2018/12/12.
62. Newnham ED, Shepherd SJ, Strauss BJ, Hosking P, Gibson PR. Adherence to the gluten-free diet can achieve the therapeutic goals in almost all patients with coeliac disease: A 5-year longitudinal study from diagnosis. Journal of gastroenterology and hepatology. 2016;31(2):342-9. Epub 2015/07/28.
63. Aziz I, Evans KE, Papageorgiou V, Sanders DS. Are patients with coeliac disease seeking alternative therapies to a gluten-free diet? Journal of gastrointestinal and liver diseases : JGLD. 2011;20(1):27-31. Epub 2011/04/01.
64. Freeman HJ. Dietary compliance in celiac disease. World journal of gastroenterology. 2017;23(15):2635-9. Epub 2017/05/11.
65. Vaquero L, Rodriguez-Martin L, Leon F, Jorquera F, Vivas S. New coeliac disease treatments and their complications. Gastroenterologia y hepatologia. 2018;41(3):191-204. Epub 2018/02/10. Nuevas terapias en la enfermedad celiaca y sus complicaciones.
66. Carroccio A, Di Prima L, Noto D, Fayer F, Ambrosiano G, Villanacci V, et al. Searching for wheat plants with low toxicity in celiac disease: Between direct toxicity and immunologic activation. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2011;43(1):34-9. Epub 2010/06/18.
67. Zanini B, Villanacci V, De Leo L, Lanzini A. Triticum monococcum in patients with celiac disease: a phase II open study on safety of prolonged daily administration. European journal of nutrition. 2015;54(6):1027-9. Epub 2015/04/05.
68. Zanini B, Petroboni B, Not T, Di Toro N, Villanacci V, Lanzarotto F, et al. Search for atoxic cereals: a single blind, cross-over study on the safety of a single dose of Triticum monococcum, in patients with celiac disease. BMC gastroenterology. 2013;13:92. Epub 2013/05/28.
69. Vaquero L, Comino I, Vivas S, Rodriguez-Martin L, Gimenez MJ, Pastor J, et al. Tritordeum: a novel cereal for food processing with good acceptability and significant reduction in gluten immunogenic peptides in comparison with wheat. Journal of the science of food and agriculture. 2018;98(6):2201-9. Epub 2017/10/01.
70. Frisoni M, Corazza GR, Lafiandra D, De Ambrogio E, Filipponi C, Bonvicini F, et al. Wheat deficient in gliadins: promising tool for treatment of coeliac disease. Gut. 1995;36(3):375-8. Epub 1995/03/01.
71. Zandonadi RP, Botelho RB, Araujo WM. Psyllium as a substitute for gluten in bread. Journal of the American Dietetic Association. 2009;109(10):1781-4. Epub 2009/09/29.
72. Troncone R, Ivarsson A, Szajewska H, Mearin ML. Review article: future research on coeliac disease - a position report from the European multistakeholder platform on coeliac disease (CDEUSSA). Alimentary pharmacology & therapeutics. 2008;27(11):1030-43. Epub 2008/03/05.
73. Zhang Y, Hu M, Liu Q, Sun L, Chen X, Lv L, et al. Deletion of high-molecular-weight glutenin subunits in wheat significantly reduced dough strength and bread-baking quality. BMC plant biology. 2018;18(1):319. Epub 2018/12/05.

74. van Herpen TW, Goryunova SV, van der Schoot J, Mitreva M, Salentijn E, Vorst O, et al. Alpha-gliadin genes from the A, B, and D genomes of wheat contain different sets of celiac disease epitopes. BMC genomics. 2006;7:1. Epub 2006/01/13.
75. Haro C, Villatoro M, Vaquero L, Pastor J, Gimenez MJ, Ozuna CV, et al. The Dietary Intervention of Transgenic Low-Gliadin Wheat Bread in Patients with Non-Celiac Gluten Sensitivity (NCGS) Showed No Differences with Gluten-Free Diet (GFD) but Provides Better Gut Microbiota Profile. Nutrients. 2018;10(12). Epub 2018/12/14.
76. Mukherjee R, Kelly CP, Schuppan D. Nondietary therapies for celiac disease. Gastrointestinal endoscopy clinics of North America. 2012;22(4):811-31. Epub 2012/10/23.
77. Di Cagno R, De Angelis M, Auricchio S, Greco L, Clarke C, De Vincenzi M, et al. Sourdough bread made from wheat and nontoxic flours and started with selected lactobacilli is tolerated in celiac sprue patients. Applied and environmental microbiology. 2004;70(2):1088-96. Epub 2004/02/10.
78. Rizzello CG, De Angelis M, Di Cagno R, Camarca A, Silano M, Losito I, et al. Highly efficient gluten degradation by lactobacilli and fungal proteases during food processing: new perspectives for celiac disease. Applied and environmental microbiology. 2007;73(14):4499-507. Epub 2007/05/22.
79. Yokoyama K, Nio N, Kikuchi Y. Properties and applications of microbial transglutaminase. Applied microbiology and biotechnology. 2004;64(4):447-54. Epub 2004/01/24.
80. Aaron L, Torsten M. Microbial transglutaminase: A new potential player in celiac disease. Clin Immunol. 2018. Epub 2018/12/14.
81. Santhi D, Kalaikannan A, Malairaj P, Arun Prabhu S. Application of microbial transglutaminase in meat foods: A review. Critical reviews in food science and nutrition. 2017;57(10):2071-6. Epub 2015/04/22.
82. Sollid LM, Khosla C. Novel therapies for coeliac disease. Journal of internal medicine. 2011;269(6):604-13. Epub 2011/03/16.
83. Stepniak D, Spaenij-Dekking L, Mitea C, Moester M, de Ru A, Baak-Pablo R, et al. Highly efficient gluten degradation with a newly identified prolyl endoprotease: implications for celiac disease. American journal of physiology Gastrointestinal and liver physiology. 2006;291(4):G621-9. Epub 2006/05/13.
84. Shetty R, Vestergaard M, Jessen F, Hagglund P, Knorr V, Koehler P, et al. Discovery, cloning and characterisation of proline specific prolyl endopeptidase, a gluten degrading thermo-stable enzyme from Sphaerobacter thermophiles. Enzyme and microbial technology. 2017;107:57-63. Epub 2017/09/14.
85. Veeraraghavan G, Leffler DA, Kaswala DH, Mukherjee R. Celiac disease 2015 update: new therapies. Expert review of gastroenterology & hepatology. 2015;9(7):913-27. Epub 2015/04/14.
86. 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(1):25-32. Epub 2007/05/12.
87. Kocadag Kocazorbaz E, Zihnioglu F. Purification, characterization and the use of recombinant prolyl oligopeptidase from Myxococcus xanthus for gluten hydrolysis. Protein expression and purification. 2017;129:101-7. Epub 2016/10/04.
88. Bethune MT, Khosla C. Oral enzyme therapy for celiac sprue. Methods in enzymology. 2012;502:241-71. Epub 2012/01/03.
89. Pyle GG, Paaso B, Anderson BE, Allen D, Marti T, Khosla C, et al. Low-dose gluten challenge in celiac sprue: malabsorptive and antibody responses. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2005;3(7):679-86. Epub 2005/10/07.
90. 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(2):472-80. Epub 2007/08/08.

91. Crespo-Perez L, Castillejo-de-Villasante G, Cano-Ruiz A, Leon F. Non-dietary therapeutic clinical trials in coeliac disease. European journal of internal medicine. 2012;23(1):9-14. Epub 2011/12/14.
92. Siegel M, Garber ME, Spencer AG, Botwick W, Kumar P, Williams RN, et al. Safety, tolerability, and activity of ALV003: results from two phase 1 single, escalating dose clinical trials. Digestive diseases and sciences. 2012;57(2):440-50. Epub 2011/09/29.
93. Lahdeaho ML, Kaukinen K, Laurila K, Vuotikka P, Koivurova OP, Karja-Lahdensuu T, et al. Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease. Gastroenterology. 2014;146(7):1649-58. Epub 2014/03/04.
94. Tack GJ, van de Water JM, Bruins MJ, Kooy-Winkelaar EM, van Bergen J, Bonnet P, et al. Consumption of gluten with gluten-degrading enzyme by celiac patients: a pilot-study. World journal of gastroenterology. 2013;19(35):5837-47. Epub 2013/10/15.
95. Liang L, Pinier M, Leroux JC, Subirade M. Interaction of alpha-gliadin with polyanions: design considerations for sequestrants used in supportive treatment of celiac disease. Biopolymers. 2010;93(5):418-28. Epub 2009/11/19.
96. Liang L, Pinier M, Leroux JC, Subirade M. Interaction of alpha-gliadin with poly(HEMA-co-SS): structural characterization and biological implication. Biopolymers. 2009;91(2):169-78. Epub 2008/11/01.
97. Pinier M, Verdu EF, Nasser-Eddine M, David CS, Vezina A, Rivard N, et al. Polymeric binders suppress gliadin-induced toxicity in the intestinal epithelium. Gastroenterology. 2009;136(1):288-98. Epub 2008/11/11.
98. Maynard-Smith M, Ahern H, McGlashan J, Nugent P, Ling R, Denton H, et al. Recombinant antigens based on toxins A and B of Clostridium difficile that evoke a potent toxin-neutralising immune response. Vaccine. 2014;32(6):700-5. Epub 2013/12/18.
99. Bauer MP, Numan-Ruberg SC, Bredewold OW, Kuijper EJ, Mooi-Kokenberg EA, Debast SB, et al. [Recurrence of Clostridium difficile-associated diarrhoea prevented by the administration of a whey concentrate from specifically immunised cows; prospective study]. Nederlands tijdschrift voor geneeskunde. 2008;152(35):1919-26. Epub 2008/09/24. Recidieven van Clostridium difficile-geassocieerde diarree voorkomen door toediening van een weiconcentraat van specifiek geimmuniseerde koeien; prospectief onderzoek.
100. Kurada S, Yadav A, Leffler DA. Current and novel therapeutic strategies in celiac disease. Expert review of clinical pharmacology. 2016;9(9):1211-23. Epub 2016/06/21.
101. Sample DA, Sunwoo HH, Huynh HQ, Rylance HL, Robert CL, Xu BW, et al. AGY, a Novel Egg Yolk-Derived Anti-gliadin Antibody, Is Safe for Patients with Celiac Disease. Digestive diseases and sciences. 2017;62(5):1277-85. Epub 2016/12/31.
102. Giacomin P, Zakrzewski M, Jenkins TP, Su X, Al-Hallaf R, Croese J, et al. Changes in duodenal tissue-associated microbiota following hookworm infection and consecutive gluten challenges in humans with coeliac disease. Scientific reports. 2016;6:36797. Epub 2016/11/09.
103. Bager P, Arnved J, Ronborg S, Wohlfahrt J, Poulsen LK, Westergaard T, et al. Trichuris suis ova therapy for allergic rhinitis: a randomized, double-blind, placebo-controlled clinical trial. The Journal of allergy and clinical immunology. 2010;125(1):123-30 e1-3. Epub 2009/10/06.
104. Daveson AJ, Jones DM, Gaze S, McSorley H, Clouston A, Pascoe A, et al. Effect of hookworm infection on wheat challenge in celiac disease--a randomised double-blinded placebo controlled trial. PloS one. 2011;6(3):e17366. Epub 2011/03/17.
105. Caenepeel C, Van Assche G. Whipping Crohn's With Helminth Therapies? Not Yet. Journal of Crohn's & colitis. 2017;11(4):387-9. Epub 2017/02/17.
106. Croese J, Giacomin P, Navarro S, Clouston A, McCann L, Dougall A, et al. Experimental hookworm infection and gluten microchallenge promote tolerance in celiac disease. The Journal of allergy and clinical immunology. 2015;135(2):508-16. Epub 2014/09/25.
107. Marietta EV, David CS, Murray JA. Important lessons derived from animal models of celiac disease. International reviews of immunology. 2011;30(4):197-206. Epub 2011/07/27.

108. Maurano F, Siciliano RA, De Giulio B, Luongo D, Mazzeo MF, Troncone R, et al. Intranasal administration of one alpha gliadin can downregulate the immune response to whole gliadin in mice. Scandinavian journal of immunology. 2001;53(3):290-5. Epub 2001/03/17.
109. Senger S, Luongo D, Maurano F, Mazzeo MF, Siciliano RA, Gianfrani C, et al. Intranasal administration of a recombinant alpha-gliadin down-regulates the immune response to wheat gliadin in DQ8 transgenic mice. Immunology letters. 2003;88(2):127-34. Epub 2003/07/26.
110. Di Sabatino A, Lenti MV, Corazza GR, Gianfrani C. Vaccine Immunotherapy for Celiac Disease. Frontiers in medicine. 2018;5:187. Epub 2018/07/13.
111. de Kauwe AL, Chen Z, Anderson RP, Keech CL, Price JD, Wijburg O, et al. Resistance to celiac disease in humanized HLA-DR3-DQ2-transgenic mice expressing specific anti-gliadin CD4+ T cells. J Immunol. 2009;182(12):7440-50. Epub 2009/06/06.
112. Goel G, King T, Daveson AJ, Andrews JM, Krishnarajah J, Krause R, et al. Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: two randomised, double-blind, placebo-controlled phase 1 studies. The lancet Gastroenterology & hepatology. 2017;2(7):479-93. Epub 2017/05/17.
113. Di Sabatino A, Corazza GR. Epitope-specific immunotherapy: a vaccine for coeliac disease? The lancet Gastroenterology & hepatology. 2017;2(7):464-5. Epub 2017/05/17.
114. Sapone A, de Magistris L, Pietzak M, Clemente MG, Tripathi A, Cucca F, et al. Zonulin upregulation is associated with increased gut permeability in subjects with type 1 diabetes and their relatives. Diabetes. 2006;55(5):1443-9. Epub 2006/04/29.
115. Forster C. Tight junctions and the modulation of barrier function in disease. Histochemistry and cell biology. 2008;130(1):55-70. Epub 2008/04/17.
116. Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. Lancet. 2000;355(9214):1518-9. Epub 2000/05/09.
117. Lammers KM, Lu R, Brownley J, Lu B, Gerard C, Thomas K, et al. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. Gastroenterology. 2008;135(1):194-204 e3. Epub 2008/05/20.
118. Tripathi A, Lammers KM, Goldblum S, Shea-Donohue T, Netzel-Arnett S, Buzza MS, et al. Identification of human zonulin, a physiological modulator of tight junctions, as prehaptoglobin-2. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(39):16799-804. Epub 2009/10/07.
119. 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. Alimentary pharmacology & therapeutics. 2007;26(5):757-66. Epub 2007/08/19.
120. Khaleghi S, Ju JM, Lamba A, Murray JA. The potential utility of tight junction regulation in celiac disease: focus on larazotide acetate. Therapeutic advances in gastroenterology. 2016;9(1):37-49. Epub 2016/01/16.
121. Kelly CP, Green PH, Murray JA, Dimarino A, Colatrella A, Leffler DA, et al. Larazotide acetate in patients with coeliac disease undergoing a gluten challenge: a randomised placebo-controlled study. Alimentary pharmacology & therapeutics. 2013;37(2):252-62. Epub 2012/11/21.
122. Leffler DA, Kelly CP, Abdallah HZ, Colatrella AM, Harris LA, Leon F, et al. A randomized, double-blind study of larazotide acetate to prevent the activation of celiac disease during gluten challenge. The American journal of gastroenterology. 2012;107(10):1554-62. Epub 2012/07/25.
123. Leffler DA, Kelly CP, Green PH, Fedorak RN, DiMarino A, Perrow W, et al. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: a randomized controlled trial. Gastroenterology. 2015;148(7):1311-9 e6. Epub 2015/02/17.
124. Rauhavirta T, Oittinen M, Kivisto R, Mannisto PT, Garcia-Horsman JA, Wang Z, et al. Are transglutaminase 2 inhibitors able to reduce gliadin-induced toxicity related to celiac disease? A proof-of-concept study. Journal of clinical immunology. 2013;33(1):134-42. Epub 2012/08/11.

~~125. Szondy Z, Sarang Z, Molnar P, Nemeth T, Piacentini M, Mastroberardino PG, et al. Transglutaminase 2 -/- mice reveal a phagocytosis-associated crosstalk between macrophages and apoptotic cells. Proceedings of the National Academy of Sciences of the United States of America. 2003;100(13):7812-7. Epub 2003/06/18.~~

~~126. Xia J, Bergseng E, Fleckenstein B, Siegel M, Kim CY, Khosla C, et al. Cyclic and dimeric gluten peptide analogues inhibiting DQ2-mediated antigen presentation in celiac disease. Bioorganic & medicinal chemistry. 2007;15(20):6565-73. Epub 2007/08/08.~~

~~127. Booth V, Keizer DW, Kamphuis MB, Clark-Lewis I, Sykes BD. The CXCR3 binding chemokine IP-10/CXCL10: structure and receptor interactions. Biochemistry. 2002;41(33):10418-25. Epub 2002/08/14.~~

~~128. Olaussen RW, Karlsson MR, Lundin KE, Jahnsen J, Brandtzaeg P, Farstad IN. Reduced chemokine receptor 9 on intraepithelial lymphocytes in celiac disease suggests persistent epithelial activation. Gastroenterology. 2007;132(7):2371-82. Epub 2007/06/16.~~

1. Murray JA, Frey MR, Oliva-Hemker M. Celiac Disease [Historical Article

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review]. Gastroenterology. 2018 Jun;154(8):2005-2008. doi: 10.1053/j.gastro.2017.12.026. PubMed PMID: 29550590; PubMed Central PMCID: PMC6203336. eng.
2. Ludvigsson JF, Rubio-Tapia A, van Dyke CT, et al. Increasing incidence of celiac disease in a North American population [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. The American journal of gastroenterology. 2013 May;108(5):818-24. doi: 10.1038/ajg.2013.60. PubMed PMID: 23511460; PubMed Central PMCID: PMC3686116. eng.
3. Rodrigo L, Garrote JA, Vivas S. [Celiac disease]. Medicina clinica. 2008 Sep 6;131(7):264-70. PubMed PMID: 18775218; spa.
4. Robert ME, Crowe SE, Burgart L, et al. Statement on Best Practices in the Use of Pathology as a Diagnostic Tool for Celiac Disease: A Guide for Clinicians and Pathologists. The American journal of surgical pathology. 2018 Sep;42(9):e44-e58. doi: 10.1097/PAS.0000000000001107. PubMed PMID: 29923907; eng.
5. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease [Research Support, N.I.H., Extramural

Review]. Gastroenterology. 2006 Dec;131(6):1981-2002. doi: 10.1053/j.gastro.2006.10.004. PubMed PMID: 17087937; eng.
6. Vaquero L, Caminero A, Nunez A, et al. Coeliac disease screening in first-degree relatives on the basis of biopsy and genetic risk [Evaluation Studies

Research Support, Non-U.S. Gov't]. European journal of gastroenterology & hepatology. 2014 Mar;26(3):263-7. doi: 10.1097/MEG.0000000000000020. PubMed PMID: 24300305; eng.
7. Vaquero L, Rodriguez-Martin L, Alvarez-Cuenllas B, et al. Coeliac Disease and Gastrointestinal Symptom Screening in Adult First-degree Relatives. Journal of

gastroenterology and hepatology. 2017 Apr 07. doi: 10.1111/jgh.13801. PubMed PMID: 28387454; eng.
8. Vaquero L, Rodriguez-Martin L, Hernando M, et al. Duodenal mucosa FOXP3 expression in different etiologies of lymphocytic duodenosis. Histology and histopathology. 2017 Mar 10:11888. doi: 10.14670/HH-11-888. PubMed PMID: 28281276; eng.
9. Vaquero L, Alvarez-Cuenllas B, Rodriguez-Martin L, et al. [A review of diseases related to the intake of gluten] [Review]. Nutricion hospitalaria. 2015 Jun 01;31(6):2359-71. doi: 10.3305/nh.2015.31.6.8984. PubMed PMID: 26040340; spa.
10. Rubio-Tapia A, Rahim MW, See JA, et al. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet [Research Support, N.I.H., Extramural]. The American journal of gastroenterology. 2010 Jun;105(6):1412-20. doi: 10.1038/ajg.2010.10. PubMed PMID: 20145607; PubMed Central PMCID: PMC2881171. eng.
11. Lebwohl B, Granath F, Ekbom A, et al. Mucosal healing and mortality in coeliac disease [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. Alimentary pharmacology & therapeutics. 2013 Feb;37(3):332-9. doi: 10.1111/apt.12164. PubMed PMID: 23190299; PubMed Central PMCID: PMC3566869. eng.
12. Theethira TG, Dennis M, Leffler DA. Nutritional consequences of celiac disease and the gluten-free diet [Research Support, Non-U.S. Gov't]. Expert review of gastroenterology & hepatology. 2014 Feb;8(2):123-9. doi: 10.1586/17474124.2014.876360. PubMed PMID: 24417260; eng.
13. Theethira TG, Dennis M. Celiac disease and the gluten-free diet: consequences and recommendations for improvement [Review]. Dig Dis. 2015;33(2):175-82. doi: 10.1159/000369504. PubMed PMID: 25925920; eng.
14. Lanzini A, Lanzarotto F, Villanacci V, et al. Complete recovery of intestinal mucosa occurs very rarely in adult coeliac patients despite adherence to gluten-free diet. Alimentary pharmacology & therapeutics. 2009 Jun 15;29(12):1299-308. doi: 10.1111/j.1365-2036.2009.03992.x. PubMed PMID: 19302264; eng.
15. Barratt SM, Leeds JS, Sanders DS. Quality of life in Coeliac Disease is determined by perceived degree of difficulty adhering to a gluten-free diet, not the level of dietary adherence ultimately achieved. Journal of gastrointestinal and liver diseases : JGLD. 2011 Sep;20(3):241-5. PubMed PMID: 21961090; eng.
16. Vaquero L, Alvarado MG, Arias L, et al. [Enteropathy-associated intestinal t-cell lymphoma without celiac disease] [Case Reports]. Gastroenterologia y hepatologia. 2012 Jan;35(1):17-21. doi: 10.1016/j.gastrohep.2011.11.003. PubMed PMID: 22177267; spa.
17. Vivas S, Ruiz de Morales JM, Ramos F, et al. Alemtuzumab for refractory celiac disease in a patient at risk for enteropathy-associated T-cell lymphoma [Case Reports

Letter]. The New England journal of medicine. 2006 Jun 8;354(23):2514-5. doi: 10.1056/NEJMc053129. PubMed PMID: 16760460; eng.
18. Comino I, Moreno Mde L, Sousa C. Role of oats in celiac disease [Review]. World journal of gastroenterology. 2015 Nov 7;21(41):11825-31. doi: 10.3748/wjg.v21.i41.11825. PubMed PMID: 26557006; PubMed Central PMCID: PMC4631980. eng.
19. Comino I, Real A, de Lorenzo L, et al. Diversity in oat potential immunogenicity: basis for the selection of oat varieties with no toxicity in coeliac disease [Research Support, Non-U.S. Gov't]. Gut. 2011 Jul;60(7):915-22. doi: 10.1136/gut.2010.225268. PubMed PMID: 21317420; PubMed Central PMCID: PMC3112367. eng.
20. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review]. Gastroenterology. 2009 Dec;137(6):1912-33. doi: 10.1053/j.gastro.2009.09.008. PubMed PMID: 19766641; eng.

21. Maiuri L, Ciacci C, Ricciardelli I, et al. Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease [Research Support, Non-U.S. Gov't]. Lancet. 2003 Jul 5;362(9377):30-7. doi: 10.1016/S0140-6736(03)13803-2. PubMed PMID: 12853196; eng.
22. Di Sabatino A, Giuffrida P, Fornasa G, et al. Innate and adaptive immunity in self-reported nonceliac gluten sensitivity versus celiac disease [Comparative Study]. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2016 Jul;48(7):745-52. doi: 10.1016/j.dld.2016.03.024. PubMed PMID: 27130911; eng.
23. Montalvillo E, Bernardo D, Martinez-Abad B, et al. Increased Intraepithelial Valpha24 Invariant NKT Cells in the Celiac Duodenum [Research Support, Non-U.S. Gov't]. Nutrients. 2015 Oct 30;7(11):8960-76. doi: 10.3390/nu7115444. PubMed PMID: 26529008; PubMed Central PMCID: PMC4663572. eng.
24. Beckett CG, Dell'Olio D, Shidrawi RG, et al. Gluten-induced nitric oxide and pro-inflammatory cytokine release by cultured coeliac small intestinal biopsies [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. European journal of gastroenterology & hepatology. 1999 May;11(5):529-35. PubMed PMID: 10755257; eng.

25. Murray IA, Daniels I, Coupland K, et al. Increased activity and expression of iNOS in human duodenal enterocytes from patients with celiac disease. American journal of physiology Gastrointestinal and liver physiology. 2002 Aug;283(2):G319-26. doi: 10.1152/ajpgi.00324.2001. PubMed PMID: 12121878; eng.
26. Daniels I, Cavill D, Murray IA, et al. Elevated expression of iNOS mRNA and protein in coeliac disease. Clinica chimica acta; international journal of clinical chemistry. 2005 Jun;356(1-2):134-42. doi: 10.1016/j.cccn.2005.01.029. PubMed PMID: 15936309; eng.
27. De Stefano D, Maiuri MC, Iovine B, et al. The role of NF-kappaB, IRF-1, and STAT-1alpha transcription factors in the iNOS gene induction by gliadin and IFN-gamma in RAW 264.7 macrophages. J Mol Med (Berl). 2006 Jan;84(1):65-74. doi: 10.1007/s00109-005-0713-x. PubMed PMID: 16284791; eng.
28. Martin-Pagola A, Perez-Nanclares G, Ortiz L, et al. MICA response to gliadin in intestinal mucosa from celiac patients [Research Support, Non-U.S. Gov't]. Immunogenetics. 2004 Nov;56(8):549-54. doi: 10.1007/s00251-004-0724-8. PubMed PMID: 15490153; eng.
29. Clemente MG, De Virgiliis S, Kang JS, et al. Early effects of gliadin on enterocyte intracellular signalling involved in intestinal barrier function [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. Gut. 2003 Feb;52(2):218-23. PubMed PMID: 12524403; PubMed Central PMCID: PMC1774976. eng.

30. Sander GR, Cummins AG, Henshall T, et al. Rapid disruption of intestinal barrier function by gliadin involves altered expression of apical junctional proteins. FEBS letters. 2005 Aug 29;579(21):4851-5. doi: 10.1016/j.febslet.2005.07.066. PubMed PMID: 16099460; eng.
31. Barone MV, Zanzi D, Maglio M, et al. Gliadin-mediated proliferation and innate immune activation in celiac disease are due to alterations in vesicular trafficking [Research Support, Non-U.S. Gov't]. PloS one. 2011 Feb 25;6(2):e17039. doi: 10.1371/journal.pone.0017039. PubMed PMID: 21364874; PubMed Central PMCID: PMC3045409. eng.

32. Di Sabatino A, Ciccocioppo R, Cupelli F, et al. Epithelium derived interleukin 15 regulates intraepithelial lymphocyte Th1 cytokine production, cytotoxicity, and survival in coeliac disease. Gut. 2006 Apr;55(4):469-77. doi: 10.1136/gut.2005.068684. PubMed PMID: 16105889; PubMed Central PMCID: PMC1856172. eng.
33. Meresse B, Chen Z, Ciszewski C, et al. Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. Immunity. 2004 Sep;21(3):357-66. doi: 10.1016/j.immuni.2004.06.020. PubMed PMID: 15357947; eng.
34. Hue S, Mention JJ, Monteiro RC, et al. A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease [Research Support, Non-U.S. Gov't]. Immunity. 2004 Sep;21(3):367-77. doi: 10.1016/j.immuni.2004.06.018. PubMed PMID: 15357948; eng.
35. Escudero-Hernandez C, Pena AS, Bernardo D. Immunogenetic Pathogenesis of Celiac Disease and Non-celiac Gluten Sensitivity [Review]. Current gastroenterology reports. 2016 Jul;18(7):36. doi: 10.1007/s11894-016-0512-2. PubMed PMID: 27216895; eng.
36. Raki M, Tollefsen S, Molberg O, et al. A unique dendritic cell subset accumulates in the celiac lesion and efficiently activates gluten-reactive T cells [Comparative Study

Research Support, Non-U.S. Gov't]. Gastroenterology. 2006 Aug;131(2):428-38. doi: 10.1053/j.gastro.2006.06.002. PubMed PMID: 16890596; eng.
37. Yoshimura S, Bondeson J, Brennan FM, et al. Role of NFkappaB in antigen presentation and development of regulatory T cells elucidated by treatment of dendritic cells with the proteasome inhibitor PSI [Research Support, Non-U.S. Gov't]. European journal of immunology. 2001 Jun;31(6):1883-93. PubMed PMID: 11433385; eng.
38. Ouaaz F, Arron J, Zheng Y, et al. Dendritic cell development and survival require distinct NF-kappaB subunits [Research Support, U.S. Gov't, P.H.S.]. Immunity. 2002 Feb;16(2):257-70. PubMed PMID: 11869686; eng.
39. Ohteki T, Tada H, Ishida K, et al. Essential roles of DC-derived IL-15 as a mediator of inflammatory responses in vivo [Comparative Study

Research Support, Non-U.S. Gov't]. The Journal of experimental medicine. 2006 Oct 2;203(10):2329-38. doi: 10.1084/jem.20061297. PubMed PMID: 16966429; PubMed Central PMCID: PMC2118106. eng.
40. Pabst O, Mowat AM. Oral tolerance to food protein [Research Support, Non-U.S. Gov't

Review]. Mucosal immunology. 2012 May;5(3):232-9. doi: 10.1038/mi.2012.4. PubMed PMID: 22318493; PubMed Central PMCID: PMC3328017. eng.
41. Mowat AM. Anatomical basis of tolerance and immunity to intestinal antigens [Review]. Nature reviews Immunology. 2003 Apr;3(4):331-41. doi: 10.1038/nri1057. PubMed PMID: 12669023; eng.
42. Karell K, Louka AS, Moodie SJ, et al. HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease [Research Support, Non-U.S. Gov't]. Human immunology. 2003 Apr;64(4):469-77. PubMed PMID: 12651074; eng.
43. Anderson RP, Degano P, Godkin AJ, et al. In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope [Research Support, Non-U.S. Gov't]. Nature medicine. 2000 Mar;6(3):337-42. doi: 10.1038/73200. PubMed PMID: 10700238; eng.
44. Arentz-Hansen H, McAdam SN, Molberg O, et al. Celiac lesion T cells recognize epitopes that cluster in regions of gliadins rich in proline residues [Research Support, Non-U.S. Gov't]. Gastroenterology. 2002 Sep;123(3):803-9. PubMed PMID: 12198706; eng.

45. Nilsen EM, Jahnsen FL, Lundin KE, et al. Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease [Research Support, Non-U.S. Gov't]. Gastroenterology. 1998 Sep;115(3):551-63. PubMed PMID: 9721152; eng.
46. Leon AJ, Garrote JA, Blanco-Quiros A, et al. Interleukin 18 maintains a long-standing inflammation in coeliac disease patients [Research Support, Non-U.S. Gov't]. Clinical and experimental immunology. 2006 Dec;146(3):479-85. doi: 10.1111/j.1365-2249.2006.03239.x. PubMed PMID: 17100768; PubMed Central PMCID: PMC1810422. eng.
47. MacDonald TT, Bajaj-Elliott M, Pender SL. T cells orchestrate intestinal mucosal shape and integrity [Research Support, Non-U.S. Gov't

Review]. Immunology today. 1999 Nov;20(11):505-10. PubMed PMID: 10529778; eng.
48. Jabri B, Kasarda DD, Green PH. Innate and adaptive immunity: the yin and yang of celiac disease [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Review]. Immunological reviews. 2005 Aug;206:219-31. doi: 10.1111/j.0105-2896.2005.00294.x. PubMed PMID: 16048552; eng.
49. Jabri B, Sollid LM. Mechanisms of disease: immunopathogenesis of celiac disease [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review]. Nature clinical practice Gastroenterology & hepatology. 2006 Sep;3(9):516-25. doi: 10.1038/ncpgasthep0582. PubMed PMID: 16951668; eng.
50. Londei M, Ciacci C, Ricciardelli I, et al. Gliadin as a stimulator of innate responses in celiac disease [Review]. Molecular immunology. 2005 May;42(8):913-8. doi: 10.1016/j.molimm.2004.12.005. PubMed PMID: 15829281; eng.
51. Gianfrani C, Auricchio S, Troncone R. Adaptive and innate immune responses in celiac disease [Review]. Immunology letters. 2005 Jul 15;99(2):141-5. doi: 10.1016/j.imlet.2005.02.017. PubMed PMID: 15876458; eng.
52. Koning F. Celiac disease: caught between a rock and a hard place [Research Support, Non-U.S. Gov't

Review]. Gastroenterology. 2005 Oct;129(4):1294-301. doi: 10.1053/j.gastro.2005.07.030. PubMed PMID: 16230082; eng.
53. Koning F, Gilissen L, Wijmenga C. Gluten: a two-edged sword. Immunopathogenesis of celiac disease [Review]. Springer seminars in immunopathology. 2005 Sep;27(2):217-32. doi: 10.1007/s00281-005-0203-9. PubMed PMID: 16091925; eng.
54. Tye-Din JA, Galipeau HJ, Agardh D. Celiac Disease: A Review of Current Concepts in Pathogenesis, Prevention, and Novel Therapies [Review]. Frontiers in pediatrics. 2018;6:350. doi: 10.3389/fped.2018.00350. PubMed PMID: 30519552; PubMed Central PMCID: PMC6258800. eng.
55. Halmos EP, Clarke D, Pizzey C, et al. Gluten in "gluten-free" manufactured foods in Australia: a cross-sectional study. The Medical journal of Australia. 2018 Nov 19;209(10):448-449. PubMed PMID: 30404591; eng.
56. C D, Berry N, Vaiphei K, et al. Quality of life in celiac disease and the effect of gluten-free diet. JGH open : an open access journal of gastroenterology and hepatology. 2018 Aug;2(4):124-128. doi: 10.1002/jgh3.12056. PubMed PMID: 30483576; PubMed Central PMCID: PMC6207046. eng.

57. Reilly NR, Lebwohl B, Hultcrantz R, et al. Increased risk of non-alcoholic fatty liver disease after diagnosis of celiac disease [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. Journal of hepatology. 2015 Jun;62(6):1405-11. doi: 10.1016/j.jhep.2015.01.013. PubMed PMID: 25617505; PubMed Central PMCID: PMC4439270. eng.

58. Lebwohl B, Cao Y, Zong G, et al. Long term gluten consumption in adults without celiac disease and risk of coronary heart disease: prospective cohort study. BMJ. 2017 May 2;357:j1892. doi: 10.1136/bmj.j1892. PubMed PMID: 28465308; PubMed Central PMCID: PMC5421459 at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work apart from the grant support noted above; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. eng.

59. Rashtak S, Murray JA. Review article: coeliac disease, new approaches to therapy [Research Support, N.I.H., Extramural

Review]. Alimentary pharmacology & therapeutics. 2012 Apr;35(7):768-81. doi: 10.1111/j.1365-2036.2012.05013.x. PubMed PMID: 22324389; PubMed Central PMCID: PMC3912561. eng.

60. Akobeng AK, Thomas AG. Systematic review: tolerable amount of gluten for people with coeliac disease [Research Support, Non-U.S. Gov't

Review

Systematic Review]. Alimentary pharmacology & therapeutics. 2008 Jun 1;27(11):1044-52. doi: 10.1111/j.1365-2036.2008.03669.x. PubMed PMID: 18315587; eng.

61. Schiepatti A, Bellani V, Perlato M, et al. Inadvertent and minimal gluten intake has a negligible role in the onset of symptoms in patients with coeliac disease on a gluten-free diet. The British journal of nutrition. 2018 Dec 11:1-23. doi: 10.1017/S0007114518003616. PubMed PMID: 30526695; eng.

62. Newnham ED, Shepherd SJ, Strauss BJ, et al. Adherence to the gluten-free diet can achieve the therapeutic goals in almost all patients with coeliac disease: A 5-year longitudinal study from diagnosis [Research Support, Non-U.S. Gov't]. Journal of gastroenterology and hepatology. 2016 Feb;31(2):342-9. doi: 10.1111/jgh.13060. PubMed PMID: 26212198; eng.

63. Aziz I, Evans KE, Papageorgiou V, et al. Are patients with coeliac disease seeking alternative therapies to a gluten-free diet? Journal of gastrointestinal and liver diseases : JGLD. 2011 Mar;20(1):27-31. PubMed PMID: 21451794; eng.

64. Freeman HJ. Dietary compliance in celiac disease [Editorial]. World journal of gastroenterology. 2017 Apr 21;23(15):2635-2639. doi: 10.3748/wjg.v23.i15.2635. PubMed PMID: 28487600; PubMed Central PMCID: PMC5403742. eng.

65. Vaquero L, Rodriguez-Martin L, Leon F, et al. New coeliac disease treatments and their complications [Review]. Gastroenterologia y hepatologia. 2018 Mar;41(3):191-204. doi: 10.1016/j.gastrohep.2017.12.002. PubMed PMID: 29422237; eng

spa.

66. Carroccio A, Di Prima L, Noto D, et al. Searching for wheat plants with low toxicity in celiac disease: Between direct toxicity and immunologic activation [Research Support, Non-U.S. Gov't]. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2011 Jan;43(1):34-9. doi: 10.1016/j.dld.2010.05.005. PubMed PMID: 20554485; eng.

67. Zanini B, Villanacci V, De Leo L, et al. Triticum monococcum in patients with celiac disease: a phase II open study on safety of prolonged daily administration. European journal of nutrition. 2015 Sep;54(6):1027-9. doi: 10.1007/s00394-015-0892-3. PubMed PMID: 25840666; eng.
68. Zanini B, Petroboni B, Not T, et al. Search for atoxic cereals: a single blind, cross-over study on the safety of a single dose of Triticum monococcum, in patients with celiac disease [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. BMC gastroenterology. 2013;13:92. doi: 10.1186/1471-230X-13-92. PubMed PMID: 23706063; PubMed Central PMCID: PMC3664588. eng.
69. Vaquero L, Comino I, Vivas S, et al. Tritordeum: a novel cereal for food processing with good acceptability and significant reduction in gluten immunogenic peptides in comparison with wheat. Journal of the science of food and agriculture. 2018 Apr;98(6):2201-2209. doi: 10.1002/jsfa.8705. PubMed PMID: 28963718; eng.
70. Frisoni M, Corazza GR, Lafiandra D, et al. Wheat deficient in gliadins: promising tool for treatment of coeliac disease [Comparative Study]. Gut. 1995 Mar;36(3):375-8. PubMed PMID: 7698695; PubMed Central PMCID: PMC1382448. eng.
71. Zandonadi RP, Botelho RB, Araujo WM. Psyllium as a substitute for gluten in bread [Comparative Study]. Journal of the American Dietetic Association. 2009 Oct;109(10):1781-4. doi: 10.1016/j.jada.2009.07.032. PubMed PMID: 19782179; eng.
72. Troncone R, Ivarsson A, Szajewska H, et al. Review article: future research on coeliac disease - a position report from the European multistakeholder platform on coeliac disease (CDEUSSA) [Research Support, Non-U.S. Gov't

Review]. Alimentary pharmacology & therapeutics. 2008 Jun 1;27(11):1030-43. doi: 10.1111/j.1365-2036.2008.03668.x. PubMed PMID: 18315588; eng.
73. Zhang Y, Hu M, Liu Q, et al. Deletion of high-molecular-weight glutenin subunits in wheat significantly reduced dough strength and bread-baking quality. BMC plant biology. 2018 Dec 3;18(1):319. doi: 10.1186/s12870-018-1530-z. PubMed PMID: 30509162; PubMed Central PMCID: PMC6276161. eng.
74. van Herpen TW, Goryunova SV, van der Schoot J, et al. Alpha-gliadin genes from the A, B, and D genomes of wheat contain different sets of celiac disease epitopes [Comparative Study

Research Support, Non-U.S. Gov't]. BMC genomics. 2006 Jan 10;7:1. doi: 10.1186/1471-2164-7-1. PubMed PMID: 16403227; PubMed Central PMCID: PMC1368968. eng.
75. Haro C, Villatoro M, Vaquero L, et al. The Dietary Intervention of Transgenic Low-Gliadin Wheat Bread in Patients with Non-Celiac Gluten Sensitivity (NCGS) Showed No Differences with Gluten Free Diet (GFD) but Provides Better Gut Microbiota Profile. Nutrients. 2018 Dec 12;10(12). doi: 10.3390/nu10121964. PubMed PMID: 30545051; eng.
76. Mukherjee R, Kelly CP, Schuppan D. Nondietary therapies for celiac disease [Research Support, Non-U.S. Gov't

Review]. Gastrointestinal endoscopy clinics of North America. 2012 Oct;22(4):811-31. doi: 10.1016/j.giec.2012.09.001. PubMed PMID: 23083995; eng.
77. Di Cagno R, De Angelis M, Auricchio S, et al. Sourdough bread made from wheat and nontoxic flours and started with selected lactobacilli is tolerated in celiac sprue patients [Clinical Trial

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. Applied and environmental microbiology. 2004 Feb;70(2):1088-96. PubMed PMID: 14766592; PubMed Central PMCID: PMC348803. eng.
78. Rizzello CG, De Angelis M, Di Cagno R, et al. Highly efficient gluten degradation by lactobacilli and fungal proteases during food processing: new perspectives for celiac disease [Research Support, Non-U.S. Gov't]. Applied and environmental microbiology. 2007 Jul;73(14):4499-507. doi: 10.1128/AEM.00260-07. PubMed PMID: 17513580; PubMed Central PMCID: PMC1932817. eng.
79. Yokoyama K, Nio N, Kikuchi Y. Properties and applications of microbial transglutaminase [Review]. Applied microbiology and biotechnology. 2004 May;64(4):447-54. doi: 10.1007/s00253-003-1539-5. PubMed PMID: 14740191; eng.
80. Aaron L, Torsten M. Microbial transglutaminase: A new potential player in celiac disease. Clin Immunol. 2018 Dec 10. doi: 10.1016/j.clim.2018.12.008. PubMed PMID: 30543926; eng.
81. Santhi D, Kalaikannan A, Malairaj P, et al. Application of microbial transglutaminase in meat foods: A review [Review]. Critical reviews in food science and nutrition. 2017 Jul 3;57(10):2071-2076. doi: 10.1080/10408398.2014.945990. PubMed PMID: 25897817; eng.
82. Sollid LM, Khosla C. Novel therapies for coeliac disease [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review]. Journal of internal medicine. 2011 Jun;269(6):604-13. doi: 10.1111/j.1365-2796.2011.02376.x. PubMed PMID: 21401739; PubMed Central PMCID: PMC3101315. eng.
83. Stepniak D, Spaenij-Dekking L, Mitea C, et al. Highly efficient gluten degradation with a newly identified prolyl endoprotease: implications for celiac disease [Research Support, Non-U.S. Gov't]. American journal of physiology Gastrointestinal and liver physiology. 2006 Oct;291(4):G621-9. doi: 10.1152/ajpgi.00034.2006. PubMed PMID: 16690904; eng.
84. Shetty R, Vestergaard M, Jessen F, et al. Discovery, cloning and characterisation of proline specific prolyl endopeptidase, a gluten degrading thermo-stable enzyme from Sphaerobacter thermophiles. Enzyme and microbial technology. 2017 Dec;107:57-63. doi: 10.1016/j.enzmictec.2017.08.002. PubMed PMID: 28899487; eng.
85. Veeraraghavan G, Leffler DA, Kaswala DH, et al. Celiac disease 2015 update: new therapies [Research Support, Non-U.S. Gov't

Review]. Expert review of gastroenterology & hepatology. 2015 Jul;9(7):913-27. doi: 10.1586/17474124.2015.1033399. PubMed PMID: 25864708; eng.
86. Mitea C, Havenaar R, Drijfhout JW, et al. Efficient degradation of gluten by a prolyl endoprotease in a gastrointestinal model: implications for coeliac disease [Research Support, Non-U.S. Gov't]. Gut. 2008 Jan;57(1):25-32. doi: 10.1136/gut.2006.111609. PubMed PMID: 17494108; eng.
87. Kocadag Kocazorbaz E, Zihnioglu F. Purification, characterization and the use of recombinant prolyl oligopeptidase from Myxococcus xanthus for gluten hydrolysis [Research Support, Non-U.S. Gov't]. Protein expression and purification. 2017 Jan;129:101-107. doi: 10.1016/j.pep.2016.09.016. PubMed PMID: 27693621; eng.
88. Bethune MT, Khosla C. Oral enzyme therapy for celiac sprue. Methods in enzymology. 2012;502:241-71. doi: 10.1016/B978-0-12-416039-2.00013-6. PubMed PMID: 22208988; PubMed Central PMCID: PMC3382113. eng.
89. Pyle GG, Paaso B, Anderson BE, et al. Effect of pretreatment of food gluten with prolyl endopeptidase on gluten-induced malabsorption in celiac sprue [Clinical Trial

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2005 Jul;3(7):687-94. PubMed PMID: 16206502; eng.

90. Gass J, Bethune MT, Siegel M, et al. Combination enzyme therapy for gastric digestion of dietary gluten in patients with celiac sprue [Research Support, N.I.H., Extramural]. Gastroenterology. 2007 Aug;133(2):472-80. doi: 10.1053/j.gastro.2007.05.028. PubMed PMID: 17681168; eng.
91. Crespo Perez L, Castillejo de Villasante G, Cano Ruiz A, et al. Non-dietary therapeutic clinical trials in coeliac disease [Review]. European journal of internal medicine. 2012 Jan;23(1):9-14. doi: 10.1016/j.ejim.2011.08.030. PubMed PMID: 22153524; eng.
92. Siegel M, Garber ME, Spencer AG, et al. Safety, tolerability, and activity of ALV003: results from two phase 1 single, escalating-dose clinical trials [Clinical Trial, Phase I]. Digestive diseases and sciences. 2012 Feb;57(2):440-50. doi: 10.1007/s10620-011-1906-5. PubMed PMID: 21948339; eng.
93. Tye-Din JA, Anderson RP, Ffrench RA, et al. The effects of ALV003 pre-digestion of gluten on immune response and symptoms in celiac disease in vivo [Randomized Controlled Trial]. Clin Immunol. 2010 Mar;134(3):289-95. doi: 10.1016/j.clim.2009.11.001. PubMed PMID: 19942485; eng.
94. Lahdeaho ML, Kaukinen K, Laurila K, et al. Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. Gastroenterology. 2014 Jun;146(7):1649-58. doi: 10.1053/j.gastro.2014.02.031. PubMed PMID: 24583059; eng.

95. Murray JA, Kelly CP, Green PHR, et al. No Difference Between Latiglutenase and Placebo in Reducing Villous Atrophy or Improving Symptoms in Patients With Symptomatic Celiac Disease [Clinical Trial, Phase II

Multicenter Study

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. Gastroenterology. 2017 Mar;152(4):787-798 e2. doi: 10.1053/j.gastro.2016.11.004. PubMed PMID: 27864127; eng.

96. Syage JA, Murray JA, Green PHR, et al. Latiglutenase Improves Symptoms in Seropositive Celiac Disease Patients While on a Gluten-Free Diet [Multicenter Study

Randomized Controlled Trial

Research Support, Non-U.S. Gov't

Research Support, N.I.H., Extramural]. Digestive diseases and sciences. 2017 Sep;62(9):2428-2432. doi: 10.1007/s10620-017-4687-7. PubMed PMID: 28755266; PubMed Central PMCID: PMC5709215. eng.

97. Syage JA, Kelly CP, Dickason MA, et al. Determination of gluten consumption in celiac disease patients on a gluten-free diet [Research Support, Non-U.S. Gov't]. The American journal of clinical nutrition. 2018 Feb 1;107(2):201-207. doi: 10.1093/ajcn/nqx049. PubMed PMID: 29529159; eng.
98. Tack GJ, van de Water JM, Bruins MJ, et al. Consumption of gluten with gluten-degrading enzyme by celiac patients: a pilot-study [Randomized Controlled Trial]. World journal of gastroenterology. 2013 Sep 21;19(35):5837-47. doi: 10.3748/wjg.v19.i35.5837. PubMed PMID: 24124328; PubMed Central PMCID: PMC3793137. eng.
99. Wolf C, Siegel JB, Tinberg C, et al. Engineering of Kuma030: A Gliadin Peptidase That Rapidly Degrades Immunogenic Gliadin Peptides in Gastric Conditions [Research

Support, Non-U.S. Gov't]. Journal of the American Chemical Society. 2015 Oct 14;137(40):13106-13. doi: 10.1021/jacs.5b08325. PubMed PMID: 26374198; PubMed Central PMCID: PMC4958374. eng.

100. Liang L, Pinier M, Leroux JC, et al. Interaction of alpha-gliadin with polyanions: design considerations for sequestrants used in supportive treatment of celiac disease [Research Support, Non-U.S. Gov't]. Biopolymers. 2010 May;93(5):418-28. doi: 10.1002/bip.21352. PubMed PMID: 19921745; eng.
101. Liang L, Pinier M, Leroux JC, et al. Interaction of alpha-gliadin with poly(HEMA-co-SS): structural characterization and biological implication [Research Support, Non-U.S. Gov't]. Biopolymers. 2009 Feb;91(2):169-78. doi: 10.1002/bip.21109. PubMed PMID: 18975377; eng.
102. Pinier M, Verdu EF, Nasser-Eddine M, et al. Polymeric binders suppress gliadin-induced toxicity in the intestinal epithelium [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. Gastroenterology. 2009 Jan;136(1):288-98. doi: 10.1053/j.gastro.2008.09.016. PubMed PMID: 18992747; eng.

103. Maynard-Smith M, Ahern H, McGlashan J, et al. Recombinant antigens based on toxins A and B of Clostridium difficile that evoke a potent toxin-neutralising immune response [Research Support, Non-U.S. Gov't]. Vaccine. 2014 Feb 3;32(6):700-5. doi: 10.1016/j.vaccine.2013.11.099. PubMed PMID: 24342251; PubMed Central PMCID: PMC3969267. eng.
104. Bauer MP, Numan-Ruberg SC, Bredewold OW, et al. [Recurrence of Clostridium difficile-associated diarrhoea prevented by the administration of a whey concentrate from specifically immunised cows; prospective study] [Comment]. Nederlands tijdschrift voor geneeskunde. 2008 Aug 30;152(35):1919-26. PubMed PMID: 18808082; dut.
105. Kurada S, Yadav A, Leffler DA. Current and novel therapeutic strategies in celiac disease [Review]. Expert review of clinical pharmacology. 2016 Sep;9(9):1211-23. doi: 10.1080/17512433.2016.1200463. PubMed PMID: 27322016; eng.
106. Sample DA, Sunwoo HH, Huynh HQ, et al. AGY, a Novel Egg Yolk-Derived Anti-gliadin Antibody, Is Safe for Patients with Celiac Disease [Research Support, Non-U.S. Gov't]. Digestive diseases and sciences. 2017 May;62(5):1277-1285. doi: 10.1007/s10620-016-4426-5. PubMed PMID: 28035551; eng.
107. Giacomin P, Zakrzewski M, Jenkins TP, et al. Changes in duodenal tissue-associated microbiota following hookworm infection and consecutive gluten challenges in humans with coeliac disease [Research Support, Non-U.S. Gov't]. Scientific reports. 2016 Nov 9;6:36797. doi: 10.1038/srep36797. PubMed PMID: 27827438; PubMed Central PMCID: PMC5101533. eng.
108. Bager P, Arnved J, Ronborg S, et al. Trichuris suis ova therapy for allergic rhinitis: a randomized, double-blind, placebo-controlled clinical trial [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. The Journal of allergy and clinical immunology. 2010 Jan;125(1):123-30 e1-3. doi: 10.1016/j.jaci.2009.08.006. PubMed PMID: 19800680; eng.

109. Daveson AJ, Jones DM, Gaze S, et al. Effect of hookworm infection on wheat challenge in celiac disease--a randomised double-blinded placebo controlled trial [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. PloS one. 2011 Mar 8;6(3):e17366. doi: 10.1371/journal.pone.0017366. PubMed PMID: 21408161; PubMed Central PMCID: PMC3050888. eng.

110. Caenepeel C, Van Assche G. Whipping Crohn's With Helminth Therapies? Not Yet. J Crohns Colitis. 2017 Apr 1;11(4):387-389. doi: 10.1093/ecco-jcc/jjx007. PubMed PMID: 28204053; eng.

111. Croese J, Giacomin P, Navarro S, et al. Experimental hookworm infection and gluten microchallenge promote tolerance in celiac disease [Research Support, Non-U.S. Gov't]. The Journal of allergy and clinical immunology. 2015 Feb;135(2):508-16. doi: 10.1016/j.jaci.2014.07.022. PubMed PMID: 25248819; eng.
112. Marietta EV, David CS, Murray JA. Important lessons derived from animal models of celiac disease [Research Support, N.I.H., Extramural

Review]. International reviews of immunology. 2011 Aug;30(4):197-206. doi: 10.3109/08830185.2011.598978. PubMed PMID: 21787225; PubMed Central PMCID: PMC3480308. eng.
113. Maurano F, Siciliano RA, De Giulio B, et al. Intranasal administration of one alpha gliadin can downregulate the immune response to whole gliadin in mice [Research Support, Non-U.S. Gov't]. Scandinavian journal of immunology. 2001 Mar;53(3):290-5. PubMed PMID: 11251887; eng.
114. Senger S, Luongo D, Maurano F, et al. Intranasal administration of a recombinant alpha-gliadin down-regulates the immune response to wheat gliadin in DQ8 transgenic mice. Immunology letters. 2003 Aug 5;88(2):127-34. PubMed PMID: 12880682; eng.
115. Di Sabatino A, Lenti MV, Corazza GR, et al. Vaccine Immunotherapy for Celiac Disease. Frontiers in medicine. 2018;5:187. doi: 10.3389/fmed.2018.00187. PubMed PMID: 29998106; PubMed Central PMCID: PMC6028606. eng.
116. de Kauwe AL, Chen Z, Anderson RP, et al. Resistance to celiac disease in humanized HLA-DR3-DQ2-transgenic mice expressing specific anti-gliadin CD4+ T cells [Research Support, Non-U.S. Gov't]. J Immunol. 2009 Jun 15;182(12):7440-50. doi: 10.4049/jimmunol.0900233. PubMed PMID: 19494267; eng.
117. Goel G, King T, Daveson AJ, et al. Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: two randomised, double-blind, placebo-controlled phase 1 studies [Clinical Trial, Phase I

Multicenter Study

Randomized Controlled Trial

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. The lancet Gastroenterology & hepatology. 2017 Jul;2(7):479-493. doi: 10.1016/S2468-1253(17)30110-3. PubMed PMID: 28506538; PubMed Central PMCID: PMC5676538. eng.
118. Di Sabatino A, Corazza GR. Epitope-specific immunotherapy: a vaccine for coeliac disease? [Comment]. The lancet Gastroenterology & hepatology. 2017 Jul;2(7):464-465. doi: 10.1016/S2468-1253(17)30141-3. PubMed PMID: 28506537; eng.
119. Sapone A, de Magistris L, Pietzak M, et al. Zonulin upregulation is associated with increased gut permeability in subjects with type 1 diabetes and their relatives. Diabetes. 2006 May;55(5):1443-9. PubMed PMID: 16644703; eng.
120. Forster C. Tight junctions and the modulation of barrier function in disease [Research Support, Non-U.S. Gov't

Review]. Histochemistry and cell biology. 2008 Jul;130(1):55-70. doi: 10.1007/s00418-008-0424-9. PubMed PMID: 18415116; PubMed Central PMCID: PMC2413111. eng.
121. Fasano A, Not T, Wang W, et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease [Letter

Research Support, U.S. Gov't, P.H.S.]. Lancet. 2000 Apr 29;355(9214):1518-9. doi: 10.1016/S0140-6736(00)02169-3. PubMed PMID: 10801176; eng.

122. Lammers KM, Lu R, Brownley J, et al. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3 [Research Support, N.I.H., Extramural]. Gastroenterology. 2008 Jul;135(1):194-204 e3. doi: 10.1053/j.gastro.2008.03.023. PubMed PMID: 18485912; PubMed Central PMCID: PMC2653457. eng.
123. Tripathi A, Lammers KM, Goldblum S, et al. Identification of human zonulin, a physiological modulator of tight junctions, as prehaptoglobin-2 [Research Support, N.I.H., Extramural]. Proceedings of the National Academy of Sciences of the United States of America. 2009 Sep 29;106(39):16799-804. doi: 10.1073/pnas.0906773106. PubMed PMID: 19805376; PubMed Central PMCID: PMC2744629. eng.
124. Paterson BM, Lammers KM, Arrieta MC, et al. The safety, tolerance, pharmacokinetic and pharmacodynamic effects of single doses of AT-1001 in coeliac disease subjects: a proof of concept study [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. Alimentary pharmacology & therapeutics. 2007 Sep 1;26(5):757-66. doi: 10.1111/j.1365-2036.2007.03413.x. PubMed PMID: 17697209; eng.
125. Khaleghi S, Ju JM, Lamba A, et al. The potential utility of tight junction regulation in celiac disease: focus on larazotide acetate [Review]. Therapeutic advances in gastroenterology. 2016 Jan;9(1):37-49. doi: 10.1177/1756283X15616576. PubMed PMID: 26770266; PubMed Central PMCID: PMC4699279. eng.
126. Kelly CP, Green PH, Murray JA, et al. Larazotide acetate in patients with coeliac disease undergoing a gluten challenge: a randomised placebo-controlled study [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. Alimentary pharmacology & therapeutics. 2013 Jan;37(2):252-62. doi: 10.1111/apt.12147. PubMed PMID: 23163616; eng.
127. Leffler DA, Kelly CP, Abdallah HZ, et al. A randomized, double-blind study of larazotide acetate to prevent the activation of celiac disease during gluten challenge [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. The American journal of gastroenterology. 2012 Oct;107(10):1554-62. doi: 10.1038/ajg.2012.211. PubMed PMID: 22825365; PubMed Central PMCID: PMC3463856. eng.
128. Leffler DA, Kelly CP, Green PH, et al. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: a randomized controlled trial [Clinical Trial, Phase II

Multicenter Study

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. Gastroenterology. 2015 Jun;148(7):1311-9 e6. doi: 10.1053/j.gastro.2015.02.008. PubMed PMID: 25683116; PubMed Central PMCID: PMC4446229. eng.
129. Rauhavirta T, Oittinen M, Kivisto R, et al. Are transglutaminase 2 inhibitors able to reduce gliadin-induced toxicity related to celiac disease? A proof-of-concept study [Research Support, Non-U.S. Gov't]. Journal of clinical immunology. 2013 Jan;33(1):134-42. doi: 10.1007/s10875-012-9745-5. PubMed PMID: 22878839; eng.
130. Szondy Z, Sarang Z, Molnar P, et al. Transglutaminase 2-/- mice reveal a phagocytosis-associated crosstalk between macrophages and apoptotic cells [Research Support, Non-U.S. Gov't]. Proceedings of the National Academy of Sciences of the United States of America. 2003 Jun 24;100(13):7812-7. doi: 10.1073/pnas.0832466100. PubMed PMID: 12810961; PubMed Central PMCID: PMC164670. eng.

131. Xia J, Bergseng E, Fleckenstein B, et al. Cyclic and dimeric gluten peptide analogues inhibiting DQ2-mediated antigen presentation in celiac disease [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. Bioorganic & medicinal chemistry. 2007 Oct 15;15(20):6565-73. doi: 10.1016/j.bmc.2007.07.001. PubMed PMID: 17681795; PubMed Central PMCID: PMC2034199. eng.

132. Olaussen RW, Karlsson MR, Lundin KE, et al. Reduced chemokine receptor 9 on intraepithelial lymphocytes in celiac disease suggests persistent epithelial activation [Research Support, Non-U.S. Gov't]. Gastroenterology. 2007 Jun;132(7):2371-82. doi: 10.1053/j.gastro.2007.04.023. PubMed PMID: 17570212; eng.