Chapter 6

Celiac Treatments, Adjuvant Therapies and Alternatives to the Gluten-Free Diet

Justin L. McCarville, Alberto Caminero, Elena F. Verdu

Farncombe Family Digestive Health Research Institute; McMaster University; Hamilton, ON Canada.

mccarvjl@mcmaster.ca, acamine@mcmaster.ca, verdue@mcmaster.ca

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Abstract

Celiac disease (CD) is a chronic enteropathy triggered by exposure to dietary gluten in genetically susceptible individuals. The only currently accepted therapy for CD is a lifetime gluten-free diet (GFD). Although a GFD has proven to be a safe and effective in most celiac patients, there are limitations that warrant new adjuvant therapies for the treatment of CD. The therapies in development for CD fall into the following categories 1) Gluten detoxification 2) Luminal therapies 3) Intestinal barrier enhancing therapies 4) Immune targeted therapies and 5) Experimental therapies. Gluten detoxification includes altering gluten proteins in foods before commercialization. Luminal therapies aim at neutralizing gluten in the lumen of the small intestine. These include enzymatic digestion therapy, probiotics and gluten binders. Barrier enhancing therapies decrease the leaky intestinal condition associated with the disease, which could enhance translocation of gluten peptides, or of other harmful antigens, into the lamina propria. Immune targeted therapies include TG2 blockers, HLA blockers, T cell targeted therapies, alteration of inflammatory mediators and vaccine therapy. Finally, experimental therapies comprise compounds or biological strategies in discovery phase. Of these, Elafin was recently proposed to play a role in CD and have potential therapeutic applications in an animal model. To date, none of the discussed therapies have been approved for clinical use and are at different stages of development. However, adjuvant therapies to the GFD will likely become a reality to the coming years and will increase the quality of life of patients living with gluten-related disorders.

Keywords

Therapies for CD, gluten free alternatives, celiac therapies, gluten detoxification, gluten proteolysis.

1. Introduction

Celiac disease (CD) is a chronic autoimmune enteropathy triggered by exposure to dietary gluten in genetically susceptible individuals. Patients with a diagnosis of CD need to adopt a strict gluten-free diet (GFD) for life[1]. A GFD leads to significant clinical and histological improvement in CD patients, although it often results in social burden. This diet is expensive, not readily available in many countries, and if not properly supervised, may lead to nutritional deficiencies, which can affect the patient's quality of life. A gluten-containing diet based on consumption of cereals such as wheat, rye and barley is an important source of iron, dietary fibre and vitamin B[2-4]. A major problem underlying compliance with the GFD resides in the difficulty of complete avoidance of gluten[5] since its presence in processed foods, as well as its use in cosmetics and pharmaceutical industries, is ubiquitous. Gluten may be present in non-starchy foodstuff such as soy sauce and beer, and thus CD patients can be exposed inadvertently to small amounts of gluten that generate inflammation[6]. Furthermore, studies have shown that mucosal recovery is not immediate upon the start of a GFD, and that a substantial proportion of CD patients exhibit long-lasting low-grade inflammatory changes in the small intestinal mucosa[7-10]. Therefore, although a GFD has proven to be a safe and effective therapy, the limitations described above warrant that new adjuvant therapies are needed in the treatment of CD. Based on the current understanding of the pathogenesis of CD, several potential therapeutic targets are being explored and many reviews have recently been written on this topic[11-13]. The aim of this chapter is to summarize the current approaches and discuss the recent progress in the development of potential adjuvant treatments for CD.

2. Gluten Detoxification

Wheat gluten and related proteins in barley and rye trigger CD in genetically susceptible people. The complete elimination of gluten proteins contained in cereals from the diet is key to CD management[14]. Currently,

novel techniques are being developed to generate cereal varieties with lower immunogenic or toxic capacity for CD patients. Selective breeding and genetic manipulation of the disease-activating grains have been proposed to reach this goal[15-17]. The use of genetic engineering to down-regulate gene expression by RNA interference is an attractive opportunity for reducing the immunotoxic components of gluten. This technology has been applied to down-regulate the expression of gliadins and low molecular weight glutenins in bread wheat. Results have shown the usefulness of RNAi to silence specific genes corresponding to gluten proteins, which are the known sources of immunogenic peptides[18-22]. Flour from these lines may be an important breakthrough in the development of new products for the celiac community. However, additional studies, such as clinical trials in patients with gluten-related disorders are needed in order to determine whether or not the product can be consumed by the general celiac population[18, 23].

An alternative approach to detoxify gluten is the digestion of immunogenic gluten peptides with peptidases during food processing and before administration to CD patients[24]. Unlike mammalian digestive proteases, proteolytic enzymes from plants, fungi and microorganisms can hydrolyze toxic peptides in foods to amino acids or non-toxic peptides[25]. Di cagno et al. (2010) have isolated *Lactobacillus* strains from sourdough bread that showed considerable hydrolysis of gliadin during wheat sourdough fermentation and investigated a novel bread making method for the production of safe sourdoughs[26]. Similarly, Rizello et al. (2007) showed that fermentation with a complex formula of sourdough *Lactobacillus* and fungal proteases decreased the concentration of gluten considerably. This wheat flour hydrolyzed during food processing was shown to be safe for consumption by CD patients in a clinical study[27, 28]. Although results with RNA interference and proteases in sourdough fermentation are promising, one important question is how baking quality will be affected and whether widespread consumption of these foods by CD patients will be safe[14, 15, 23].

3. Luminal Therapies

3.1. Enzymatic Therapy

Gluten proteins are poorly digested in the human intestine because they are relatively resistant to human proteolytic enzymes. As a consequence, the gastrointestinal digestion of gluten leads to the generation of toxic peptides which trigger inflammation in genetically susceptible individuals[29]. Thus, oral enzymatic therapy is focused on inactivating immunogenic gluten peptides in the human gastrointestinal tract[30,31]. The most commonly studied enzymes with the ability to carry out this process are proteases from the prolyl endopeptidase family (PEPs) which are not present in humans. PEPs from *Flavobacterium meningosepticum*, *Sphingomonas capsulata* and *Myxococcus xanthus* are able to cleave immunodominant proline-rich regions present in gluten proteins[32-34].

For these enzymes to be effective, they must be resistant to both the acidic environment and digestive proteases of the stomach. Also, the majority of the epitope hydrolysis should occur in the stomach, to avoid toxic peptides entering the small intestine and triggering immune responses. Although encapsulation of PEPs was proposed in order to protect them from gastric secretions, recent studies have shown that only high doses of PEPs are capable of eliminating immunogenic peptides in a daily gluten load[35,36]. AN-PEP is an enzyme derived from *Aspergillus niger* that is being developed by an alimentary company (DSM)[37]. *In vitro* studies have shown that AN-PEP is active at acidic pH, resists digestion by pepsin and degrades all tested gluten peptides with a half-life ranging between 2 and 6 minutes[34,38]. Based on these *in vitro* findings, a number of *in vivo* studies are underway in CD patients. Although AN-PEP appears to be well tolerated in CD patients, clinical improvements in these patients are not clear[39]. (ClinicalTrials.gov Identifier: NCT01335503). Another drug candidate, ALV003, is being developed as an orally administered mixture of two glutenases (ALV001 and ALV002)[40]. ALV001 is a glutamine-specific cysteine endoprotease derived from germinating barley seeds (EP-B2) and ALV002 is a PEP from *Sphingomonas*

capsulata[33,41]. Both enzymes are active in the acidic environment of the stomach, and a 1:1 (w/w) formulation (ALV003) maximizes their glutenasic activity[33]. Phase 1 and Phase 2a clinical trials have been performed in CD patients receiving ALV003. These studies demonstrated that ALV003 can attenuate gluten-induced small intestinal mucosal injury and decrease the immune response to gluten in CD patients, but ALV003 did not improve the clinical response (NCT00959114 and NCT01255696)[42,43]. A Phase 2b, randomized, double-blind, placebo-controlled dose-ranging study of the efficacy and safety of ALV003 treatment in symptomatic CD patients maintained on a GFD is currently underway (ClinicalTrials.gov Identifier: NCT01917630). A third protease mixture (STAN 1) has been tested in a Phase 2 clinical trial (ClinicalTrials.gov Identifier: NCT00962182). STAN1 is a cocktail of microbial enzymes commonly used in food supplements that showed modest gluten detoxification capacity[31,44]. The study evaluated the effect of STAN1 in CD patients ingesting 1 g of gluten per day for 12 weeks. No differences were found in serology between the placebo group and the patients treated with STAN1[44,45]. A common setback with oral enzyme therapy seems to be the need for sufficiently active enzyme delivery to allow interaction with immunogenic gluten peptides present in a daily gluten load. However, although these enzymes may not eliminate the need for a GFD, they may provide substantial flexibility and prevention of detrimental side effects from lower gluten exposures, reducing long term complications of delayed mucosal healing[12]. A live commensal or beneficial bacterium that produces gluten-specific proteolytic molecules *in situ* would be an attractive alternative.

3.2. Probiotic Therapy

"Probiotics are defined as live microorganisms that when administered in adequate amounts confer health benefits to the host"[46]. Probiotics show a variety of immuno-modulatory, barrier enhancing and even mood-modulating effects that may be attractive to CD patients[47-49]. The probiotic preparation VSL#3 has been shown to hydrolyze gliadin proteins *in vitro* and may

produce pre-digested gliadins during food processing[50]. Other studies with cell cultures and mouse models of gluten sensitivity have demonstrated that "particular probiotic bacteria such as *Bifidobacterium lactis* or *Lactobacillus casei* could be of potential use in CD"[51-53]. Administration of a specific *Bifidobacterium infantis* strain to patients with active CD (ClinicalTrials.gov identifier: NCT01257620) led to improvement in CD-associated symptoms accompanied by immunogenic changes, without a significant change in intestinal permeability[54].

Another suggested alternative to facilitate gluten degradation and immune modulation includes the use of whole cultured bacteria from the human gastrointestinal tract. A number of studies from different groups have described substantial differences in the intestinal microbiota of patients with CD[55-57]. *Bifidobacterium longum* CECT7347 is a probiotic bacterial strain isolated from a healthy breastfed child with anti-inflammatory effects and proteolytic activity toward gliadin peptides *in vitro*[58-60]. To date, a double-bind, randomized, placebo-controlled intervention trial to evaluate the effects of *Bifidobacterium longum* CECT7347 in children with newly diagnosed CD has been completed. The findings suggest that *B. longum* CECT 7347 could help improve the health status of CD patients who tend to show alterations in gut microbiota composition and a biased immune response even on a GFD[61]. Moreover, several studies have isolated commensal bacteria strains from the human oral cavity and large intestine with the ability to hydrolyze peptides rich in proline including immunogenic peptides from gliadin such as the 33-mer and 26-mer peptide. These bacteria are candidate probiotics of interest in the treatment of CD[62,63]. For example, some *Lactobacillus* and *Bifidobacterium* strains have shown beneficial effects *in vitro* due to immunomodulation and restoration of the gliadin-induced epithelial barrier disruption[60,64]. Additional pre-clinical and clinical data are necessary to support the use of specific probiotics in CD patients.

Due to the ability of PEPs to hydrolyze gluten, Alvarez-Sieiro et al. (2014) have engineered two food-grade *Lactobacillus casei* strains to deliver PEP in a small intestinal *in vitro* model. One strain secretes PEP into the

surrounding environment, whereas the other retains PEP intracellularly. The extracellular secreting strain is the most effective at degrading the 33-mer and is resistant to simulated gastrointestinal stress. Results suggest that in the future, a genetically engineered (GMO) food-grade lactic acid bacterium may be useful as a vector for *in situ* production of PEP in the upper small intestine of CD patients[65]. This may raise discussions on the public acceptability of GMO's, despite the fact these have been shown to be safe for administration to mice and humans[66, 67].

3.3. Gluten Binding Polymer: BL-7010

The gluten binding polymer, BL-7010 or copolymer poly(hydroxythyl methacrylate-*co*-styrene sulfonate (P(HEMA-*co*-*SS*) is a non-absorbable polymer that binds with high specificity to gliadin or gluten, intraluminally. Upon binding of the polymer to gliadin, digestive enzymes are unable to access cleavage sites on the protein, thereby avoiding the production of immunogenic peptides[68]. Further, these peptides are not absorbed by the small intestine and therefore do not seem to induce immune responses in the host. BL-7010 has shown preclinical *in vitro*[69] and *in vivo* beneficial effects using a humanized mouse model of gluten sensitivity (HLA-HCD4/DQ8 mice), BL-7010 decreased gluten associated pathology, including intraepithelial lymphocytosis, reduced villus-to-crypt ratios, and normalized altered barrier function[68]. This therapy has a high safety profile in animal models and Phase 1 clinical trials are currently underway (ClinicalTrials.gov Identifier: NTC01990885).

4. Barrier Enhancing Therapies

CD is associated with altered barrier[70] and disrupted tight junction (TJ) function[71,72]. The mechanisms for gluten peptide translocation in CD are controversial, and several pathways have been proposed[73,74]. One is related to increases in paracellular uptake and increases in the release of zonulin, an endogenous modulator of TJs[75]. Zonulin has been reported to be regulated by

the direct binding of gliadin to CXCR3 in intestinal epithelial cells, increasing its release and subsequent decrease in barrier function[74]. Larazotide acetate, or AT-1001, is being developed as a TJ modulator by Alba Therapeutics. This molecule is an octapeptide derived from cholera toxin, secreted by *Vibrio cholerae*[44]. *In vitro*, larazotide acetate was shown to promote actin rearrangement and prevent disassembly of tight junctions due to external stimuli[76], including gliadin[77], in cell culture. Additionally, this small peptide inhibited translocation of gliadin constituents (13-mer) across cell culture monolayers, *in vitro*[77]. In an *in vivo* animal model using HLA-HCD4/DQ8 mice, administration of larazotide acetate normalized TJ proteins and inhibited macrophage recruitment in the intestine induced by gliadin[77]. In human trials, AT-1001 tended to improve increased intestinal permeability in CD patients upon gluten challenge compared to CD individuals who received placebo, but this did not achieve statistical significance[78]. However, larazotide acetate decreased gluten-induced gastrointestinal symptoms[79], and decreased gluten-induced INF-γ levels[78]. A follow up study demonstrated that CD patients, when on a GFD receiving a daily challenge of 2.7 grams of gluten and larazotide acetate had lower TG2 IgA levels in comparison to patients on placebo receiving the same challenge[80]. Phase 2b trial results have recently been released by ALBA Therapeutics, GI and non-GI symptoms were reduced in individuals on a GFD for more than 12 months, while taking larazotide acetate in comparison to placebo. Larazotide acetate will now enter phase 3 trials[81].

5. Immune Targeted Therapies

There are several immune therapies under development for chronic gastrointestinal inflammation that could be applied to CD. Some target CD specific pathways, other target inflammatory mediators common in gastrointestinal inflammation. For instance, drugs for the treatment of inflammatory bowel disease (IBD) could be useful in CD[44]. On the other hand, immune specific therapies for CD include transglutaminase-2 (TG2) blockers,

human leukocyte antigen (HLA) blockers, anti-IL-15 monoclonal antibodies and vaccine approaches[25].

5.1. TG2 Blockers

TG2 plays a critical role in CD pathogenesis by unmasking gluten-derived T cell epitopes via demidation[82]. Therefore it is of great interest as a therapeutic target. There have been many TG2 blockers developed, as TG2 is associated with other diseases, such as Huntington's disease and certain cancers[83]. The different subsets of TG2 inhibitors include, competitive amine inhibitors, reversible inhibitors and irreversible inhibitors[84]. The blocking of TG2 *in viv*o in humans has not been demonstrated and *in vivo* models are scarce. Therefore most studies have concentrated on *in vitro* and *in situ* models. TG2 inhibitors are capable of reducing certain gliadin-induced effects *in vitro*[85]. Further, in organ culture from CD patient biopsies, blockers are capable of reducing $CD25^+$ and $IL\text{-}15^+$ cells induced by gluten[85] and it has been shown that CD biopsies incubated with gliadin and the TG2 inhibitor cystamine, led to a reduction in the proliferation of gliadin-specific T cells[83]. Similarly, it has been demonstrated that 2-[(2-oxopropyl)thio]imidazolium inhibitor L682777 is effective at blocking T cell activation in small intestinal CD biopsies when incubated with non-deamindated gliadin[83]. ERW1041E is the only TG2 inhibitor to date, that has been shown *in vivo* to be effective at blocking TG2[86]. TG2 inhibitors may not be capable of treating innate immune responses, as shortening of villus-to-crypt ratios induced by poly (I:C) is unaffected by inhibiting TG2[86]. The biological significance of TG2 inhibitors is unknown, as TG2s exact physiological function is still unclear, however, in *in situ* and *in vitro*, no side effects have been observed[83]. However this will need to be defined before clinical trials are planned. Gianfrani et al. (2007) have proposed an enzyme strategy to inactivate immunogenic peptides and, at the same time, preserve the integrity of the protein structure using transamidation of wheat flour with a food-grade enzyme and an appropriate amine donor. The authors treated wheat flour with one microbial

transglutaminase and lysine methyl ester generating modified gliadin peptides which decreased their affinity to HLA-DQ[87].

5.2. HLA Blockers

The genetic component of CD, the HLA-DQ2/8 molecules, are required for the development the disease, making them a desirable target for therapies. HLA blockers have been attempted as a therapy in other diseases, such as multiple sclerosis and rheumatoid arthritis[25]. The major drawback of these therapies was the inability of the HLA blocker to reach the diseased site. However, the rationale for treating CD with HLA blockers is the ease of accessibility to the site of disease (small intestine)[25]. Therefore, researchers are developing molecules with similar structure to gliadin that do not elicit an immune response because they are not recognized by gluten-specific T cells. Kaporerchan et al. (2013) developed a strategy in which the proline residues of gluten were replaced with azidoprolines. This molecule binds to HLA-DQ2 decreasing immune responses in T cells isolated from individuals with CD[88]. Similarly, Xia et al. (2007) developed cyclic and dimeric peptides with the capacity to bind DQ2, partially blocking T cell proliferation and antigen presentation[84]. However, these molecules do not fully block T cell activation[25].

5.3. T cell Targeted Therapies

T cells play a critical role in the pathology of CD, being responsible for the proinflammatory immune response and villus atrophy[89]. There are no current T cell mediated therapies that are being developed specifically for CD. Anti-CD3 monoclonal antibodies could potentially block pathogenic gluten-specific T cells[25] and are currently undergoing clinical trials for diabetes and ulcerative colitis. CCR9 is a chemokine receptor on T cells and antagonists of this receptor are currently being tested in clinical trials for CD[25] and Crohn's disease[90]. The drug CCX282-B, Vercirnon, or Traficet-EN could be effective in CD, by blocking the recruitment of T cells to the intestine. Traficet-EN is currently being investigated in a phase 2a clinical trial (ClinicalTrials.gov Identifier: NCT00540657)[44].

5.4. Alteration of Inflammatory Mediators

A proportion of patients with CD have increased levels of IL-15. IL-15 plays a critical role in IEL cell activation and is an important cytokine linking the innate and adaptive immune response in CD[91,92]. Therefore, blocking the actions of IL-15 in individuals with IL-15 driven CD is an attractive target. It has been shown that destruction of the small intestine can be reversed when blocking IL-15 with a monoclonal antibody in mice *in vivo*[93]. The humanized version of this antibody has been tested in humans for T cell large granular lymphocytic leukemia with success (ClinicalTrials.gov Identifier: NCT00076180)[94]. The antibody, Hu-Mik-β-1, targets IL-2/IL-15Rβ, blocking IL-15 transpresentation[95]. Recruitment for clinical trials for Hu-Mik-β-1 in CD is underway (ClinicalTrials.gov Identifier: NCT01893775). Similarly, tofacitnib, a Jak2/3 inhibitor that blocks IL-15 signaling, reversed CD-related damage in an IL-15 transgenic mouse model[96].

5.5. Vaccine Therapy

Vaccine therapy for CD is based on the concept that immune tolerance to an antigen can be induced by repetitive exposure to that same antigen. In the case of CD, immunization with gluten epitopes would induce the expansion of regulatory T cells[97], thereby restoring oral tolerance to gluten. NEXVAX2 is being developed by ImmunsanT for the treatment of CD, and comprises the use of three gluten epitopes. These peptides were chosen based on a study by Tye-Din et al. (2010), wherein they screened a library of 16,000 peptides within wheat, barley and rye for their ability to induce and stimulate T cells isolated from the serum of CD patients on a gluten containing diet. They identified three peptides responsible for the majority of the immune responses by isolated T cells, which have been incorporated into the vaccine[98]. The vaccine requires repetitive intradermal injections and is currently in phase 1b (ClinicalTrials.gov Identifier: NCT00879749)[44,99]. NEXVAX2 is only specific to HLA-DQ2 individuals (90% of the CD population)[25,99]. Of the therapies currently in development, the vaccine approach would be curative if proven efficacious.

6. Experimental Therapies

6.1 Necator americanus

The parasite *Necator americanus* is a human gastrointestinal nematode or hookworm believed to infect over 500 million people worldwide[100]. Infection with this hookworm has no major side effects, and is associated with normal mucosal appearance in duodenal biopsies[101]. However, the development of anemia may be of concern, as the parasite feeds on host blood (0.03-0.08 mL per day)[100]. Administration of *N. americanus* infective larvae to individuals with CD has shown to suppress increased $CD4^+CD25^+Foxp3^+$ cells in serum, which are associated with CD[102]. Duodenal biopsies from individuals with CD, infected with *N. americanus* and exposed to the gliadin constituent QE65[103] had decreased ability to produce IL-2, IFN-γ and IL-17A[102]. In a separate study, *Necator americanus* was shown to resist changes in villus-to-crypt ratios, increases in IELs, IgA production towards TG2, decrease IFNγ-producing IELs and lamina propria cells, as well as increase $CD3^+CD4^+Foxp3^+$ cells in IEL compartments in CD patients after gluten challenge[104]. *N. americanus* is currently in clinical trials phase 2a (ClinicalTrials.gov Identifier: NCT00671138)[44], however compared to other developing therapies, some side effects associated with this therapy may be anticipated[105]. Patient acceptance may also be an issue. It is unclear how the decrease in serum $CD4^+CD25^+Foxp3^+$ could be of advantage in CD, as these could include T regulatory cells important for inflammatory T cell suppression.

6.2. Elafin

Elafin, an anti-inflammatory serine protease inhibitor, is decreased in the colon of patients with inflammatory bowel disease, and delivery of elafin to mice alleviated chemical-induced colitis[106]. Recently, the decreased mucosal expression of elafin in the small intestine of patients with active CD was described[92]. Also, delivery of elafin to the small intestine via the food grade bacterium *Lactobacillus lactis*, ameliorated immune and pathological

responses to gluten in a mouse model (NOD-DQ8) that develops decreased villus-to-crypt ratios, anit-gliadin and anti-tissue TG2 antibodies upon sensitization[107]. Future research will need to determine the optimal delivery mode of this molecule to humans and its clinical efficacy.

7. Discussion and Conclusion

In summary, there are many therapies being developed for CD, which target different mechanisms of the disease process. Many of these therapies are already being tested in clinical trials, others are at discovery level of development. At the time this chapter was written, the most advanced therapy in clinical trial testing was the barrier enhancing therapy, AT-1001. However, it cannot be predicted that this will be the first drug to be approved for clinical use. Even when one or more drugs for CD are approved in the future years, further testing will be required to investigate whether combination therapies are more efficacious than single therapies. For example, the enzymatic therapy ALV003 or the gluten binder BL-7010 could be used in conjunction with most other therapies currently in the pipeline. However combinations of ALV003 and BL-7010 would not be advisable, since both therapies have opposite mechanisms of action. While ALV003 increases proteolytic digestion of gluten, BL-7010 reduces the action of the digestive enzymes on the gluten molecule, and the production of immunogenic peptides. Other possible combinations may include elafin therapy if further developed, with immunomodulatory or barrier enhancing probiotics. Finally, an issue of concern is whether availability of these therapies could encourage patients to abandon the gluten-free diet. Guidelines for the “adjunctive” use of these therapies with the GFD will need to be clearly established. These drugs may also prove effective in other gluten-related disorders, and this will require further research. We are approaching exciting years in the pharmacological management of gluten-related disorders. Availability of one or more of the described therapies will increase the quality of life of patients living with gluten-related disorders.

***Table 1**. Summary of current therapies in development for CD.*

Therapy	Product	Mode of Action	Stage in Development	Reference
Luminal Therapies				
Transgenic reduced-gliadin lines of Triticum	Bread wheat with low expression of harmful gliadins	Raw material for developing food products that can be safely tolerated by CD patients	Preclinical	[18,19]
Gluten-free sourdough wheat	Sourdough lactobacilli-derived peptidases	Digestion of immunogenic gluten peptides during food processing	Preclinical	[26]
	Sourdough lactobacilli-derived peptidases in combination with fungal proteases		2a	[28]
Transamidation of gliadin	wheat flour treated with TG and lysine methyl ester	Inactivates immunogenic epitopes via the transamidation of wheat flour with a food-grade enzyme and an appropriate amino donor	Preclinical	[87]
Oral enzymatic therapy	PEP from *S.capsulata, F. meningosepticum, M. xanthus*	Hydrolysis of proline-rich peptides of gliadin in the upper gastrointestinal tract	Preclinical	[32,35]
	AN-PEP		2a	[37,39]
	ALV003		2b	[42,43]
	STAN-1		2a	
Probiotic bacteria	VSL#3	Live microorganisms that confer health benefits on the host	Preclinical	[50]
	Bifidobacterium infantis		2a	[54]
	Bifidobacterium longum CECT7347		2a	[58,59,61]

Therapy	Product	Mode of Action	Stage in Development	Reference
Gluten binding therapy	p(HEMA-*co*-SS) or BL-7010	Binds to gluten in the intestinal lumen, avoiding gluten's translocation and immune induction	Preclinical	[68]
Barrier Enhancing Therapies				
Zonulin inhibitor	AT-1001	Lazazotide acetate inhibits zonulin activation, increasing associations between tight junctions and therefore decreases intestinal permeability	2b	[80,81]
Immune Targeted Therapies				
HLA blockers	Azidoprolines/cyclic and dimeric peptides	Binders of HLA-DQ2 that block T cell proliferation and activation towards natural gluten peptides	preclinical	[84,88]
IL-15 signaling blockers	Hu-Mik-β-1	Monoclonal antibody that targets IL-2/IL-15Rβ, blocking IL-15 transpresentation	1	[93,94]
	Tofacitinib	Jak2/3 inhibitor that blocks IL-15 signaling	3 for treatment of ulcerative colitis	[96]
CCR9 antagonist	Traficet-EN	Antagonizes CCR9 on T cells, blocking their recruitment and localization to the small intestine	2a	[90]
Vaccine	NEXVAX2	Intradermal injection of 3 gluten peptides to induce tolerance in individuals harboring HLA-DQ2	1b	[44]

Therapy	Product	Mode of Action	Stage in Development	Reference
Other Therapies				
Parasitic infection	Necator americanus	Suppresses induction of $CD4^+CD25^+Foxp3^+$ T cells in serum, increases $CD3^+CD4^+Foxp3^+$ cells in IEL compartments, decreases IL-2, IFN-γ and IL-17a from small intestinal biopsies	2a	[101,104]
Elafin	*L. lactis* secreting elafin	Decreases severity of gluten-induced pathologies	Discovery	[107]

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