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MINIREVIEWS

Beyond the gluten-free diet: Innovations in celiac disease therapeutics

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Abstract

Celiac disease (CD) is an autoimmune disorder exacerbated by the ingestion of gluten in genetically susceptible individuals, leading to intestinal inflammation and damage. This chronic disease affects approximately 1% of the world's population and is a growing health challenge due to its increasing prevalence. The development of CD is a complex interaction between genetic predispositions and environmental factors, especially gluten, culminating in a dysregulated immune response. The only effective treatment at present is a strict, lifelong gluten-free diet. However, adherence to this diet is challenging and often incomplete, so research into alternative therapies has intensified. Recent advances in understanding the molecular and immunological aspects of CD have spearheaded the development of novel pharmacologic strategies that should provide more effective and manageable treatment options. This review examines the latest innovations in CD therapies. The focus is on drugs in advanced clinical phases and targeting specific signaling pathways critical to the disease pathogenesis. We discuss both quantitative strategies such as enzymatic degradation of gluten, and qualitative approaches including immunomodulation and induction of gluten tolerance. Innovative treatments currently under investigation include transglutaminase inhibitors, which prevent the modification of gluten peptides, and nanoparticle-based therapies to recalibrate the immune response. These new therapies not only promise to improve patient outcomes but are also expected to improve quality of life by reducing the burden of dietary restrictions. The integration of these new therapies could revolutionize the treatment of CD and shift the paradigm from strict dietary restrictions to a more flexible and patient-friendly therapeutic approach. This review provides a comprehensive overview of the future

prospects of CD treatment and emphasizes the importance of continued research and multidisciplinary collaboration to integrate these advances into standard clinical practice.

Key Words: Celiac disease; Gluten tolerance; Enzymatic degradation; Therapeutic advances; Transglutaminase inhibitors; Tight junction modulators

Core Tip: The landscape of celiac disease treatment is evolving beyond the traditional gluten-free diet due to the challenges of strict adherence to the diet and incomplete resolution of symptoms. This review highlights emerging therapeutic strategies, including gluten sequestration and degradation, gluten tolerance induction, tight junction modulators, transglutaminase inhibitors, lymphocyte trafficking, and homing inhibitors. These novel therapies, which target specific molecular and immune signaling pathways, promise to improve patient outcomes and quality of life by reducing dietary restrictions and addressing persistent inflammation and symptoms. Further research and multidisciplinary collaboration are critical to integrate these advances into standard clinical practice.

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INTRODUCTION

Celiac disease (CD), a chronic autoimmune small bowel enteropathy triggered by gluten ingestion in genetically predisposed individuals[1], affects approximately 1% of the global population, with an increasing incidence that has been detected worldwide[2,3]. The pathogenesis of CD involves a complex interplay between genetic predisposition and environmental factors, primarily gluten, which leads to intestinal inflammation and villous atrophy. Currently, the only effective treatment for CD is a strict, lifelong gluten-free diet (GFD), which can be challenging to adhere to, and may not fully prevent the inflammatory responses and associated complications. Recent advances in understanding the molecular and immunological aspects of CD have opened new avenues for therapeutic interventions.

This review discusses the latest advances in the development of novel therapeutic approaches in CD, summarizing drugs currently in the advanced phases of clinical evaluation, targeting specific signaling pathways involved in the pathogenesis of the disease. We also discuss the potential of these drugs to change the treatment landscape for CD by offering alternatives to the dietary approach. By analyzing recent clinical trials and new research findings, we provide a comprehensive overview of the future prospects of CD treatment and how these new drugs could improve patient outcomes and quality of life.

CURRENT CHALLENGES IN CD MANAGEMENT

Gluten refers to a subgroup of wheat proteins, comprising monomeric water-soluble gliadins and multimeric water-insoluble glutenins. It also includes, in sensum latum, secalin, hordein and avenins, which are found in rye, barley, and oats, respectively[4]. Due to its viscoelastic properties, gluten is an important and ubiquitous ingredient in the food industry. Apart from the obvious foods, *i.e.* bread or pasta, it is also found in "unlikely" ones such as soups, sauces, yogurt, and frozen foods. In addition, it can be hidden in toothpaste and lipsticks, making strict adherence to a GFD very difficult[5].

Self-reported adherence to GFD ranges from 42% to 91% in adults and is about 59% in children, depending on age at diagnosis, ethnicity, cognitive, emotional and sociocultural influences, membership of an advocacy group, and regular dietetic follow-up[6,7]. It must be underlined, however, that even patients that are following a strict GFD can ingest gluten; in fact, according to some studies, up to 70%-80% of adherent patients present gluten contamination[8,9], with an average gluten exposure of about 150 mg/day, which is much higher than the considered safe amount[10-12]. Actually, many products can be contaminated with gluten during harvesting, processing, packaging, and cooking; in addition it could be difficult to control for gluten contamination while eating at restaurants or using packaged food[13,14].

GFD is also burdened by some other problems. First, even if popularity has recently improved this matter, gluten-free products can be more expensive and difficult to find than gluten-containing ones[15]. Second, gluten-free products, to be tastier, are often high in fat and sugar content and low in fibers, vitamins, and minerals increasing, on one hand, the risk of obesity and metabolic syndrome and, on the other, the risk of deficiencies[16,17]. Additionally, there is a theoretical risk for mycotoxin exposure from corn and arsenic exposure from rice in those who restrict their diet to only a few carbohydrate sources[18,19]. Moreover, adherence to GFD can have negative effects on quality of life, leading to isolation,

anxiety, depression, psychological distress, and maladaptive food attitudes and behaviors[20-22]. Finally, despite strict GFD, up to 30% of patients report persistent symptoms[23], about 30%-60% of adults will not achieve histological recovery after 1 year on a strict GFD[24], and up to 0.5% of patients with CD will progress to refractory CD[25]. Because of all of these limitations, there has been a growing interest in non-dietary treatment options in recent years, since the marketing of additional therapies could improve the response to GFD and reduce its social limitation.

NEW STRATEGIES TO TREAT CD

The therapeutic horizon for CD is expanding beyond strict adherence to a GFD, due to advances in our understanding of pathophysiology and the emergence of new pharmacologic interventions. Gluten includes two different types of proteins, namely gliadins and glutenins; the former are regarded as the main culprit in the pathogenesis of CD, and several studies have demonstrated that different portions of alpha-gliadin can trigger immunity. Indeed, amino acids 31-43 activate the innate immunity, whereas the 33-mer targets adaptive immunity[26]. Gliadins are characterized by repeated sequences of glutamines and prolamines, which are not easily processed by human digestive enzymes. This lack of digestion is particularly evident for the 33-mer peptide in CD subjects[26], allowing this peptide to cross the epithelial barrier, be deamidated by the enzyme tissue transglutaminase 2, and bind to human leukocyte antigen (HLA)-DQ2/8 molecules on antigen-presenting cells triggering gluten-specific cluster of differentiation 4 (CD4) T cells. These cells, in turn, activate CD8 T cells that cause small-intestinal mucosal injury. All of these processes are mediated by cytokines such as interferon gamma, tumor necrosis factor alpha, interleukin 2 (IL-2), IL-21, and IL-15[27].

Elucidation of the pathogenesis of CD has led to the identification of multiple possible therapeutic targets, enabling the development of innovative treatment strategies (Figure 1). These strategies can be broadly classified into quantitative approaches, which aim to reduce the gluten load that triggers the immune response, and qualitative approaches, which aim to modulate the immune system and promote gluten tolerance. Quantitative strategies are diverse (Table 1). They include the use of exogenous peptidases to enzymatically digest gluten into non-immunogenic fragments, the sequestration of gluten peptides in the intestinal lumen to prevent their interaction with the mucosal immune system, and the reduction of intestinal permeability to prevent the translocation of immunogenic peptides. Each of these strategies aims to mitigate the antigenic stimulus underlying the pathophysiologic response in CD.

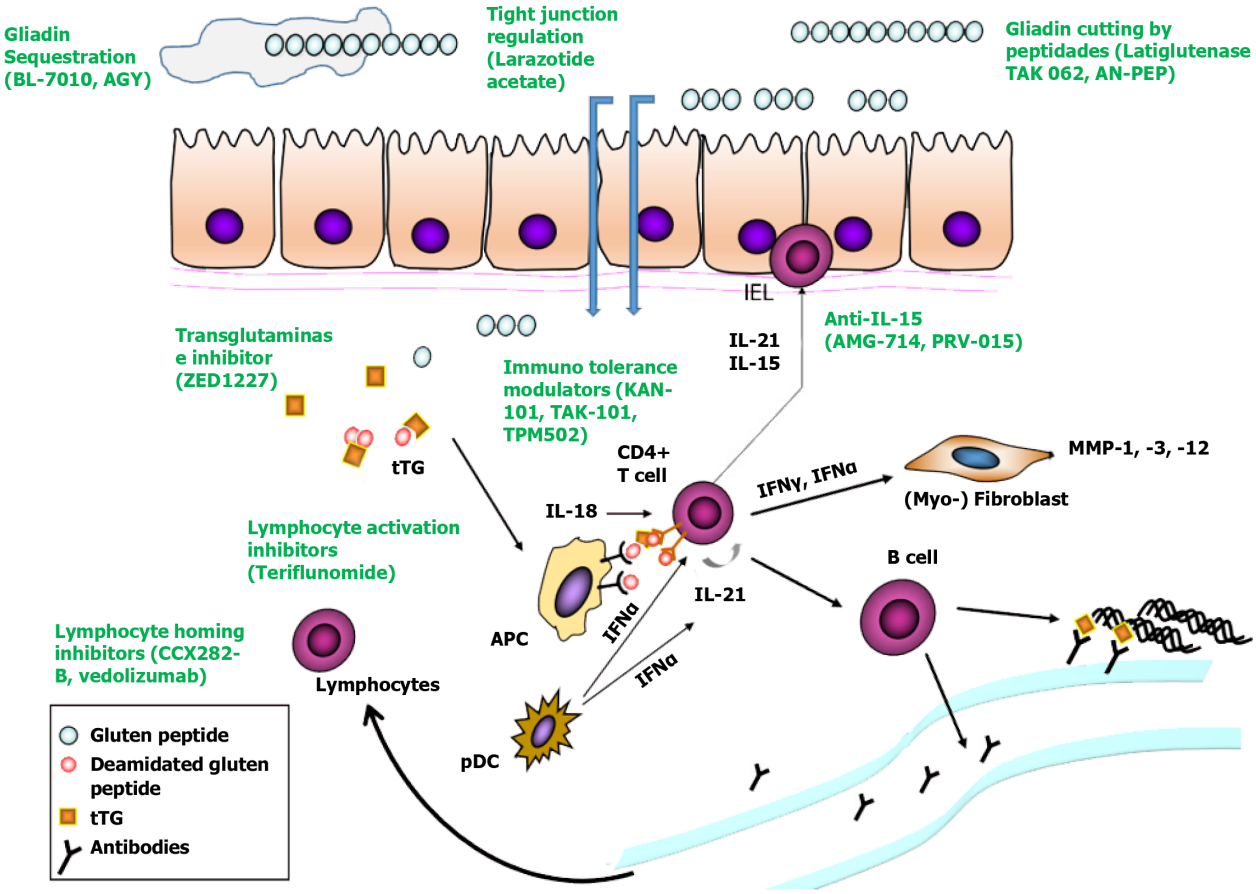

Figure 1 Mechanistic insights into innovative therapeutic approaches for celiac disease. APC: Antigen-presenting cell; IELs: Intraepithelial lymphocytes; IFN: Interferon; IL: Interleukin; MMP: Matrix metalloproteinase; pDC: Pre-dendritic cell; tTG: Tissue transglutaminase; TNF: Tumor necrosis factor.

Table 1 Phase 2 studies exploring quantitative strategies in patients with celiac disease

NCT number	Study title	Study status (completion date)	Drug	Mechanism	Primary outcome measures	Sponsor	Phases
NCT01990885	Safety and systemic exposure study of BL-7010 in patients with well-controlled CD	Completed (October 2014)	BL-7010 *vs* placebo	BL-7010 interacts with α-gliadin and prevents the formation of immunogenic and cytotoxic peptides	Incidence of adverse events. For part 1, subjects were followed for up to 7 weeks from time of first administration. For part 2, subjects were followed for up to 4 weeks from time of first administration	BioLineRx, Ltd.	Phase 1, Phase 2
NCT03707730 AGY-010	A randomized, double-blind, placebo-controlled, crossover trial to evaluate safety and efficacy of AGY in CD	Unknown (December 2022)	AGY *vs* placebo	IgY antibody put into capsule form (AGY), produced from the egg yolks of superimmunized laying hens	Safety (adverse events, laboratory results, symptoms). tTGA levels measured at each visit. CD- related symptoms 14 weeks	Igy Inc.	Phase 2
NCT01917630	Evaluation of the efficacy and safety of ALV003 in symptomatic patients with CD	Completed (June 2015)	Latiglutenase (ALV003) *vs* placebo	ALV003 is a mixture of two recombinant gluten-specific proteases to contribute to the degradation of gluten into non-immunogenic fragments	Efficacy: Intestinal mucosal morphometry, change in Vh:Cd between baseline and week 12	Alvine Pharmaceuticals Inc.	Phase 2
NCT01255696	Safety and efficacy of varying methods of ALV003 administration for the treatment of CD	Completed (June 2011)	Latiglutenase (ALV003) *vs* placebo	ALV003 is a mixture of two recombinant gluten-specific proteases to contribute to the degradation of gluten into non-immunogenic fragments	Efficacy: Intestinal mucosal morphology. Safety: Tolerability of ALV003, safety evaluated at 6 weeks	Alvine Pharmaceuticals Inc.	Phase 2
NCT00959114	Safety and efficacy of ALV003 for the treatment of CD	Completed (October 2010)	Latiglutenase (ALV003)	ALV003 is a mixture of two recombinant gluten-specific proteases to contribute to the degradation of gluten into non-immunogenic fragments	Efficacy: Intestinal mucosal morphology. Safety: Tolerability of ALV003 at 6 weeks	Alvine Pharmaceuticals Inc.	Phase 2
NCT01255696	Safety and efficacy of ALV003 for the treatment of CD	Completed (June 2011)	Latiglutenase (ALV003)	ALV003 is a mixture of two recombinant gluten-specific proteases to contribute to the degradation of gluten into non-immunogenic fragments	Efficacy: Intestinal mucosal morphology. Safety: Tolerability of ALV003 at 6 weeks	Alvine Pharmaceuticals Inc.	Phase 2
NCT03585478	Latiglutenase (IMGX003) as a treatment for CD	Completed (January 22, 2021)	Latiglutenase (IMGX003)*vs* placebo	A combination of ALV001 and ALV002, a *Sphingomonas capsulata* PEP that degrade gluten proteins and reduces the immunogenic potential of gluten	The primary efficacy endpoint of this study is histologic protection as measured by EGD (Vh:Cd) at 6 weeks	Immunogenics, LLC	Phase 2
NCT04243551	Prospective, randomized, double-blind, placebo-controlled, crossover study of latiglutenase (IMGX003) in symptomatic patients with CD	Active, not recruiting (December 2023)	Latiglutenase *vs* placebo	A combination of ALV001 and ALV002, a *Sphingomonas capsulata* PEP that degrade gluten proteins and reduces the immunogenic potential of gluten	The primary efficacy endpoint of this study is the mean percent reduction in symptom severity relative to placebo at 6 months	Immunogenics, LLC	Phase 2
NCT04839575	Study of latiglu-	Terminated	DRUG: Latiglu-	A combination of	The primary efficacy	Immunogenics	Phase 2

	tenase (IMGX003) in T1D/CD patients	(December 19 2022)	tenase *vs* placebo	ALV001 and ALV002, a *Sphingomonas capsulata* PEP that degrade gluten proteins and reduces the immunogenic potential of gluten	endpoint of this study is absolute mean reduction in symptom severity relative to placebo at 6 months	LLC	
NCT05353985	A study of TAK-062 in treatment of active CD in participants attempting a gluten-free diet	Recruiting (May 6, 2025)	TAK-062 with or without simulated inadvertent gluten exposure gluten-bar	Third-generation enzyme with the ability to degrade > 99% of gluten and gluten peptides	Change in weekly CD symptom diary gastrointestinal symptom severity score from baseline (week 1) to week 12	Takeda	Phase 2
NCT00810654	Effect of *Aspergillus Niger* prolyl endoprotease (AN-PEP) enzyme on the effects of gluten ingestion in patients with CD	Completed (2009-12)	AN-PEP 160 PPU daily for 2 weeks	An enzyme that degrades both whole gluten and gluten peptides into non-immunogenic residues within minutes	Histopathological changes according to the modified marsh criteria. The presence of CD-specific antibodies (EMA, tTGA, gliadin) (1 week before start, and 2 and 6 weeks after start)	Amsterdam UMC, location VUmc	Phase 1, phase 2

AN-PEP: *Aspergillus Niger* prolyl endoprotease; CD: Celiac disease; EGD: Esophagogastroduodenoscopy; EMA: Endomysial antibodies; IgY: Avian immunoglobulin Y; PEP: Prolyl endopeptidase; T1D: Type 1 diabetes; tTGA: Tissue transglutaminase IgA; Vh:Cd: Villous height to crypt depth ratio.

On the other hand, the qualitative approaches encompass a spectrum of modalities that alter the immune system's engagement with gluten. These include the inhibition of tissue transglutaminase, which plays a crucial role in the post-translational modification of gluten peptides, thereby reducing the formation of highly immunogenic complexes. In addition, the modulation of lymphocyte migration and homing offers an opportunity to prevent the recruitment and retention of inflammatory cells in the intestinal mucosa.

New research is also addressing the potential of desensitization to gluten through advanced biotechnological methods, such as nanoparticles engineered for targeted gliadin presentation, conjugation of gluten peptides to erythrocyte membranes, and therapeutic vaccines aimed at recalibrating the immune response. In addition, the paradigm of using helminth infestation to exploit natural pathways of immune regulation represents a novel and intriguing avenue of investigation.

EMERGING THERAPIES FROM PHASE 2 TRIALS

The pursuit of novel therapeutics in the treatment of CD has led to the initiation and progression of multiple Phase 2 clinical trials.

Gluten sequestration and degradation

Gluten sequestration and degradation strategies, with a focus on enzymatic approaches, have been extensively investigated to mitigate the effects of gluten exposure in CD. These therapeutic interventions include several notable studies (Table 1). Regarding gluten sequestration, BL-7010 is a high molecular weight, non-absorbable polymer with a high affinity for gliadin[28], which is thus able to prevent the absorption of immunogenic and cytotoxic peptides. In fact, by targeting these peptides, BL-7010 could play a crucial role in reducing the inflammatory and immunogenic responses characteristic of CD. *In vitro* studies have demonstrated that BL-7010 is effective in decreasing gliadin/gluten-induced damage in cell cultures[29]. These data have also been confirmed in a mouse model expressing HLA-HCD4/DQ8 sensitized to gluten sensitization[28-30]. This drug has been assessed in NCT01990885, a randomized, double-blind study designed to evaluate the safety of single escalating doses as well as repeated administrations of BL-7010 in patients with well-controlled CD. Although the trial took place about 10 years ago, these results have not yet been published.

Another novel approach is the use of specific antibodies, such as avian immunoglobulin Y (IgY). IgY antibodies are obtained from the egg yolks of superimmunized laying hens. These antibodies are natural products with minimal toxicity, except in people with an egg allergy. They also offer a cost-effective and hygienic method of producing therapeutic agents. When the IgY antibody is formulated in capsules, it is referred to as AGY. The idea is to use these antibodies to capture gliadin peptides present in food. The NCT01765647 trial enrolled 10 patients to evaluate the potential of AGY to relieve CD symptoms and potentially reduce the burden of strict dietary control. However, the results of this study were too weak to draw definitive conclusions. The NCT03707730 trial is a randomized, double-blind, placebo-controlled, crossover study evaluating the safety and efficacy of AGY in patients with CD on GFD. The study has enrolled 169 patients, but the data are not currently available. As aforementioned, the amino acid composition of gluten in general, and of gliadins in particular, represents a difficult task for human digestive enzymes. Thus, the quantitative reduction of food gluten content relies on enzymes derived from different sources (Table 1).

Latiglutenase is a combination of two glutenases, endoprotease B, isoform-2 (EP-B2), and *Sphingomonas capsulata* prolyl endopeptidase (SC-PEP). EP-B2 is active at low pH and has specificity for the QXP sequence, abundant both in the 31-43

and 33-mer peptides[31]. SC-PEP is a proline-specific endoprotease (PEP) that attacks the carboxy end of the gliadin peptides. The two enzymes can thus act together, with EP-B2 cutting the 33-mer peptides into smaller fragments and PEP digesting their proline-glutamine links[32]. Latiglutenase (ALV003) has been investigated in various studies. The NCT01917630 Phase 2b study examined the effects of different doses of ALV003 over 12 weeks on the small intestinal mucosa and symptoms in patients with CD. The results showed no significant differences in the primary endpoint - villous height to crypt depth (Vh:Cd) ratio - nor in secondary endpoints such as intraepithelial lymphocyte counts and serologic markers between the latiglutenase and placebo groups. A post hoc analysis[33] in a subgroup of patients still positive for autoantibodies indicated a dose-dependent reduction in symptom severity, especially at the highest dose (900 mg), suggesting potential benefits for seropositive patients.

Two other studies, *i.e.* NCT01255696 and NCT00959114, investigated the efficacy, safety, and tolerability of ALV003 in patients with well-controlled CD. In NCT00959114, patients receiving ALV003 showed no significant mucosal damage after gluten challenge (2 g bread crumbs) in contrast to the placebo group, which showed signs of mucosal deterioration. Morphological changes and the number of CD3+ intraepithelial lymphocytes showed significant differences between the groups, underlining the potential of ALV003 to mitigate gluten-induced intestinal damage[34]. Similarly, NCT01255696, a Phase 2a, double-blind, placebo-controlled study, evaluated the safety, efficacy and tolerability of 6 weeks of treatment with ALV003 in patients with well-controlled CD. In summary, these studies suggest that while ALV003 does not significantly alter histologic or serologic markers of the disease in a broad cohort, it is able to mitigate gluten-related mucosal damage in patients with CD and alleviate symptoms, particularly in seropositive individuals.

Latiglutenase was employed in three other studies: NCT03585478 was a Phase 2 double-blind, placebo-controlled study assessing the efficacy and safety of a 1200 mg dose of IMGX003 in patients with CD. Participants were treated with 2 g gluten daily for 6 weeks. The primary endpoint was the change in Vh:Cd ratio, and the results indicated a lower mean change in the Vh:Cd ratio and intraepithelial lymphocyte density for IMGX003 compared to placebo, alongside reduced symptom severity[35]. NCT04243551 is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, crossover study involving symptomatic patients with CD who had been on a GFD for at least 1 year prior to the study. The study has been completed and the results are currently awaited. NCT04839575 is a prospective, double-blind, placebo-controlled, crossover study investigating the efficacy and safety of latiglutenase treatment in patients with type 1 diabetes with CD on regular gluten exposure. It was terminated due to coronavirus disease 2019 disruptions and enrollment challenges.

TAK-062 is a computer-designed enzyme based on the bacterial kumamolisin-As, obtained from *Alicyclobacillus sendaiensis*. Interestingly, the modifications enable this enzyme to target the proline-glutamine dipeptide. Its efficacy was assessed both *in vitro* and, in Phase 1 *in vivo*, showing that it is able to degrade more than 99% of gluten in complex meals [36]. These latter data are quite interesting since the assessment of gluten degradation was demonstrated by analyzing the aspirate of the stomach content, thus in a physiological condition. NCT05353985 is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of TAK-062 in reducing CD-related symptoms and intestinal damage in CD patients attempting a GFD. The study includes two cohorts with different treatment groups receiving TAK-062 or placebo along with simulated inadvertent gluten exposure. The multicenter study, conducted across the United States, Canada, United Kingdom, and the European Union, includes adult and adolescent participants and is ongoing.

Aspergillus niger-derived prolyl endoprotease (AN-PEP) is able to cleave immunogenic gliadin peptides (behind proline residues) into smaller, non-immunogenic peptides of about eight amino acids. This enzyme is active between a pH of 2 and 8 and is resistant to pepsin; thus, it is apt to be used to degrade gliadin ingested with food[37-39]. AN-PEP was investigated in the NCT00810654[40] trial that involved only 16 adults. AN-PEP was well tolerated and there were no serious adverse events or withdrawals. The efficacy phase showed no significant worsening of CD quality scores or antibody titers in patients who consumed gluten with either placebo or AN-PEP. Histologic and immunohistochemical evaluations also indicated stability in participants taking gluten with AN-PEP. The study concluded that AN-PEP was well tolerated, but the lack of clinical differences compared to placebo made it difficult to determine the effect of the enzyme. A double-blind, randomized, placebo-controlled trial employing commercial AN-PEP on patients on GFD has recently been published[41]. Although the patients in the treatment arm showed a reduction in symptoms, no significant difference in the level of gliadin immunogenic peptide in the stools was observed, data that could be explained by the relatively low levels detected in the run-in period. Different preparations of this enzyme are already available over the counter (OTC), but their ability to digest gluten peptides can be different, and in some cases, inferior to the pure enzyme [42]. However, patients with CD should be warned of the potential risks of relying on these OTC products, as their effectiveness may not be sufficient to prevent gluten-related damage.

Gluten tolerance

These therapies are designed to induce some form of tolerance to gluten in individuals with CD, possibly through immunomodulatory mechanisms or other pathways that reduce the pathological response to gluten. This approach does not necessarily involve the direct breakdown or sequestration of gluten but instead modifies the body's response to its presence.

A first-in-human Phase 1 study (NCT04248855)[43], performed in patients with CD on GFD, evaluated the safety and tolerability of KAN-101, a synthetic liver-targeting glycopolymer that is conjugated to a synthetic deaminated peptide domain of wheat alpha gliadin designed to induce immune tolerance to gliadin. Due to the specifics of the employed peptide, this approach is reserved to individuals carrying the HLA-DQ2.5 genotype, and the drug must be administered through the intravenous route. The mechanisms detected in preclinical studies through which KAN-101 could induce immunologic tolerance include selection of antigen-specific T cells, induction of anergy of antigen-specific T cells, and induction of regulatory T cells. The study demonstrated that KAN-101 (at increasing doses of 0.15 mg/kg, 0.3 mg/kg, 0.6

mg/kg, 1.2 mg/kg, and 1.5 mg/kg) exhibited an acceptable safety profile without any dose-limiting toxicities, and no maximum tolerated dose was identified. The rapid clearance of KAN-101 from the system and the absence of accumulation with repeated doses underscore the potential for chronic use.

Two studies focusing on KAN-101 are actively recruiting (Table 2). The first study, KAN-101-03 (NCT06001177), is a multicenter, double-blind, placebo-controlled Phase 2a trial. Its primary objective is to examine the protective effects of KAN-101 against gluten-induced histological changes in the duodenum of adult participants with CD who adhere to a GFD. Additionally, the study aims to further evaluate the safety and tolerability profile of KAN-101. In parallel, study NCT05574010 adopts a two-part, multicenter Phase 1b/2 design to evaluate the effects of KAN-101 in participants with CD on a GFD. Part A consists of an open-label, multiple ascending dose assessment to determine the safety, tolerability, and pharmacokinetics of KAN-101 in adults with histologically confirmed CD. Part B progresses to a double-blind, placebo-controlled format to characterize biomarker responses post-gluten challenge, alongside further safety, tolerability, and pharmacokinetic assessments.

The investigation of gluten tolerance in CD has led to the initiation of studies on TAK-101, which consists of gliadin encapsulated in negatively charged poly(DL-lactideco-glycolic acid) nanoparticles (Table 2). These nanoparticles, intravenously injected, are taken up by positive antigen-presenting cells localized in the liver and in the spleen. The presentation of gliadin to gliadin-specific T cells can induce tolerance through anergy and the activation of regulatory T cells. The initial clinical assessment of TAK-101 involved a Phase 1 dose-escalation study (NCT03486990). The study's outcomes indicated that TAK-101 was well-tolerated, with no serious adverse events, clinically meaningful changes in vital signs or routine clinical laboratory evaluations, indicating an acceptable safety profile[36]. The double-blind, randomized, placebo-controlled Phase 2a study (NCT03738475) was pivotal in evaluating the efficacy of TAK-101 in attenuating gluten-induced immune activation in CD. Thirty-three patients on GFD underwent a 14-day gluten challenge, with the primary endpoint being the change from baseline in circulating gliadin-specific interferon gamma (IFN-g)-producing cells, which directly correlates with the pathophysiologic immune response in CD. TAK-101 administration resulted in an 88% reduction in IFN- g-producing units compared to placebo, a statistically significant finding (P = 0.006) indicating a strong immunomodulatory effect. In addition, Vh:Cd ratio analysis revealed less deterioration in the TAK-101 group compared to placebo, although the difference did not reach statistical significance. TAK-101 also showed efficacy in modulating circulating α4β7+CD4+, αEβ7+CD8+, and gδ effector memory T cells, suggesting systemic immunomodulation[44]. Further investigation of TAK-101 is being conducted in a subsequent Phase 2 study (NCT04530123), a randomized, double-blind, placebo-controlled and dose-ranging study. This study aims to evaluate the efficacy of TAK-101 in reducing gluten-related symptoms and immune activation in adult patients with CD following a GFD and undergoing a gluten challenge; its primary completion date was expected in May 2024.

Another drug aiming at inducing gluten-tolerance is TPM502, a mixture of nanoparticles carrying three peptides each consisting of two overlapping T-cell epitopes that encompass the major gluten epitopes for HLA-DQ2.5. The ongoing NCT05660109 Phase 2a study aims to evaluate its safety, tolerability, and pharmacodynamic effects according to different doses; its primary completion date was expected in May 2024 (Table 2).

Although the studies described above have provided encouraging data, Nexvax2® is among the drugs aiming at inducing tolerance. It is a gluten peptide-based antigen-specific immunotherapy that aims to desensitize and make T cells unresponsive to gluten exposure. The first Phase 1 clinical trial (NCT00879749) confirmed its bioactivity; however a following randomized clinical trial did not show any advantage in preventing intestinal damage[27,45]. Furthermore, a Phase 2 clinical trial (NCT03644069) evaluating its efficacy on patient-reported outcomes was terminated prematurely after an interim analysis because Nexvax2® was not able to reduce acute gluten-induced symptoms.

Tight junction modulators

Research into modulators of the tight junctions in CD has focused primarily on larazotide acetate, a synthetic octapeptide that reduces the permeability of tight junctions by blocking zonulin receptors, thus preventing the opening of tight junctions in the intestinal epithelium and thereby reducing the passage of gluten peptides and the consequent immune activation[46]. Changes in zonulin levels are already detectable in the very early stages of CD and could serve as early biomarkers for the disease[47,48]. In addition to zonulin-dependent mechanisms, research has also identified zonulin-independent constitutional changes in intestinal permeability in patients with CD and their first-degree relatives[47]. These inherent permeability alterations may contribute to the development and progression of CD[47,49].

However, several Phase 2 studies have investigated the efficacy and safety of larazotide (Table 3). A Phase 2b study (NCT00492960) included 184 patients on GFD[50]. Participants received larazotide acetate (1 mg, 4 mg, or 8 mg three times daily) or placebo along with 2.7 g of gluten daily for 6 weeks. Although no significant changes in the lactulose to mannitol ratio were detected, the researchers observed that the 1 mg dose of larazotide acetate significantly reduced gluten-induced symptoms, as well as the increment in anti-tissue transglutaminase antibodies caused by gluten challenge. Thus, the study suggested that larazotide acetate may reduce gluten-induced immunoreactivity and symptoms in patients with CD undergoing gluten challenge. In the NCT00362856 study, a dose-ranging, placebo-controlled study, larazotide acetate limited gluten-induced worsening of gastrointestinal symptoms at lower doses, but not at higher doses. The study concluded that while larazotide acetate has the potential to prevent the severity of gluten-induced symptoms, its effects on intestinal permeability are unclear due to the variability of lactulose to mannitol[51]. Similarly, in a double-blind, placebo-controlled Phase 2B study (NCT01396213), three doses of larazotide acetate were evaluated as an adjunct therapy to GFD in CD patients. The 0.5 mg dose of larazotide acetate significantly reduced symptoms compared to placebo. The study concluded that larazotide acetate 0.5 mg effectively reduced signs and symptoms in CD patients adhering to a GFD, representing a successful trial of a novel therapeutic agent targeting tight junction regulation[52]. Another study (NCT00620451) evaluated the efficacy of larazotide acetate in CD. This outpatient, randomized, double-blind study aimed to evaluate the efficacy of larazotide acetate in inducing remission in active CD, but did not provide

Table 2 Phase 2 studies exploring gluten tolerance strategies in patients with celiac disease

NCT number (Acronym)	Study title	Study status (Completion date)	Drug	Mechanism	Primary outcome measures	Sponsor	Phases
NCT06001177 (SynCeD)	A study of efficacy, safety, and tolerability of KAN-101 in people with CD	Recruiting (June 2025)	KAN-101 *vs* placebo	KAN-101 acts by re-educating T cells, or tolerizing them, so they do not respond to gluten antigens	Changes from baseline in Vh:Cd as assessed by esophago-gastroduodenoscopy with biopsy after 2-week gluten challenge	Kanyos Bio, Inc., a wholly-owned subsidiary of Anokion SA	Phase 2
NCT05574010 (ACeD-it)	A study of safety, tolerability, pharmaco-dynamics, and pharmacokinetics of KAN-101 in CD	Recruiting (April 2, 2025)	Part A: Multiple ascending dose of KAN-101. Parts B and C: Participants will be randomized 1:1:1:1 to placebo and 3 treatment groups with KAN-101 doses based on information obtained from part A	KAN-101 acts by re-educating T cells, or tolerizing them, so they do not respond to gluten antigens	Severity of TEAEs assessed by common terminology criteria for adverse events (part A) at 28 days. Efficacy assessed by change in magnitude of IL-2 response pre- and post-germinal center (part B), baseline to day 15	Kanyos Bio, Inc., a wholly owned subsidiary of Anokion SA	Phase 1, Phase 2
NCT03738475	Study of the safety, pharmacodynamic, efficacy, and PK of TAK-101 in subjects with CD	Completed (July 22, 2019)	TAK-101 *vs* placebo	TAK-101, gliadin encapsulated in nanoparticles to induce gluten-specific tolerance	Change from baseline in interferon gamma spot-forming units based on results of a gliadin-specific enzyme-linked immunospot on day 20	Takeda	Phase 2
NCT04530123	Dose-ranging study of the efficacy and safety of TAK-101 for prevention of gluten-specific T-cell activation in participants with CD on a gluten-free diet	Active, not recruiting (May 29, 2024)	TAK-101 with or without gluten	TAK-101, gliadin encapsulated in nanoparticles to induce gluten-specific tolerance	Change from baseline in interferon gamma spot-forming units based on results of a gliadin-specific enzyme-linked immunospot on day 20	Takeda	Phase 2
NCT05660109	A study to assess the safety of TPM502 in adults with CD	Recruiting (May 30, 2024)	Drug: TPM502. Other: Placebo	TPM502 is a mixture of nanoparticles carrying gluten-specific antigenic peptides to the liver, to induce gluten tolerization	Incidence, severity, causality, and outcomes of TEAEs throughout the study, on average 43 days	Topas Therapeutics GmbH	Phase 2
NCT03644069	A study of the safety, efficacy and tolerability of Nexvax-2 in patients with CD	Unknown (September 2019)	Nexvax2 *vs* placebo	Nexvax2 is a therapeutic vaccine that desensitizes and induces gluten tolerance	Efficacy of Nexvax2 in reducing CD-associated GI symptoms, measured by the CD patient-reported outcome between baseline and the day of the first masked food challenge containing gluten	ImmusanT, Inc.	Phase 2

CD: Celiac disease; GI: Gastrointestinal; IL: Interleukin; TEAEs: Treatment-emergent adverse events; Vh:Cd: Villous height to crypt depth ratio.

specific results. Again, the study NCT00889473, an extension of study NCT00492960, aimed to evaluate the safety, tolerability and efficacy of larazotide acetate in a gluten challenge setting. Specific results were not presented.

Overall, these studies highlight the potential of larazotide acetate as a therapeutic agent for symptomatic relief in patients adhering to a GFD. Although results were mixed regarding its effects on intestinal permeability, its ability to alleviate gluten-related symptoms seemed to offer a promising avenue for improving the quality of life of people with CD. Thus, the findings from these Phase 2 studies laid the groundwork for further exploration in Phase 3 trials.

Table 3 Phase 2 studies on tight junction modulator (larazotide acetate) in patients with celiac disease

NCT number	Study title	Study status (Completion date)	Drug	Mechanism	Primary outcome measures	Sponsor	Phases
NCT00492960	Study to assess the efficacy of larazotide acetate for the treatment of CD	Completed (March 2009)	Larazotide acetate *vs* placebo (dietary supplement: 900 mg gluten)	Larazotide acetate intervenes by blocking the zonulin receptors and thus preventing the dissolution of the tight junction and the associated increase in intestinal permeability	Efficacy of multiple doses larazotide acetate in preventing intestinal permeability changes induced by a 6-week gluten challenge on days 7, 21, 35, 49, and 56	9 Meters Biopharma Inc.	Phase 2
NCT00362856	Safety and tolerability study of larazotide acetate in patients with CD	Completed (March 6, 2007)	Larazotide *vs* placebo	Larazotide acetate intervenes by blocking the zonulin receptors and thus preventing the dissolution of the tight junction and the associated increase in intestinal permeability	Safety endpoints assessed were adverse events. Measured at screening and on days 0, 7, 14, and 21 ('End of Study'). Efficacy of multiple dose levels of larazotide acetate in preventing intestinal permeability changes induced by gluten challenge, measured as urinary LAMA ratio the day 0-to-day 14 change	9 Meters Biopharma, Inc.	Phase 2
NCT01396213	A double-blind placebo-controlled study to evaluate larazotide acetate for the treatment of CD	Completed (August 20, 2013)	Larazotide *vs* placebo	Larazotide acetate intervenes by blocking the zonulin receptors thus preventing the dissolution of the tight junction and the associated increase in intestinal permeability	The primary efficacy endpoint was the changes in the average on-treatment (baseline to week 12) score of the CD gastrointestinal symptom rating scale	9 Meters Biopharma, Inc.	Phase 2
NCT00620451	Randomized, double-blind, placebo-controlled study of larazotide acetate in subjects with active CD	Completed (December 2009)	Larazotide acetate *vs* placebo	Larazotide acetate intervenes by blocking the zonulin receptors and thus preventing the dissolution of the tight junction and the associated increase in intestinal permeability	Assess the efficacy of larazotide acetate. Remission was defined as an improvement in the Vh:Cd ratio obtained by duodenojejunal biopsy at baseline and day 56	9 Meters Biopharma, Inc.	Phase 2
NCT00889473	Study of the efficacy of larazotide acetate in CD	Completed (April 2010)	Larazotide acetate *vs* placebo (dietary supplement: gluten 900 mg)	Larazotide acetate intervenes by blocking the zonulin receptors and thus preventing the dissolution of the tight junction and the associated increase in intestinal permeability	Response to gluten at 6 weeks	9 Meters Biopharma, Inc.	Phase 2

CD: Celiac disease; LAMA: Lactulose to mannitol; Vh:Cd: Villous height to crypt depth ratio.

Transglutaminase inhibitors

Transglutaminase, modifying gluten peptides, is essential for gluten-induced T-cell activation, and the possibility to inhibit it has been widely studied. The more promising molecule in this setting is ZED 1227, assessed by Schuppan *et al* [53] in a Phase 2, double-blind, placebo-controlled trial. In this trial, 163 patients were randomly assigned to receive 10 mg ZED 1227, 50 mg ZED 1227, 100 mg ZED 1227, or placebo during gluten challenge with a moderate amount (3 g) of daily gluten intake for 6 weeks. The primary endpoint was Vh:Cd ratio, as a marker of mucosal damage. The secondary endpoints included intraepithelial lymphocyte density, the modified Marsh-Oberhuber classification, and patient-reported outcomes measured by the Celiac Symptom Index and the Celiac Disease Questionnaire. ZED1227 significantly improved Vh:Cd ratio and attenuated intraepithelial lymphocyte density dose dependently, whereas improved Celiac Symptom Index and the Celiac Disease Questionnaire independently to the dose[53]. Due to the activity of transglutaminase in several tissues, it was important to assess that the effect was limited to the intestine. For this reason, the same group assessed the loading of ZED 1227 in the biopsies of patients treated in the Phase 2 study, showing the presence of the drug mostly in the epithelium (about 80%), with only about 20% present in the lamina propria. These data also prompted the authors to hypothesize that the drug exerts its effect mainly through an inhibition at the epithelial level [54].

Lymphocytes' trafficking and homing inhibitors

Strategies for immune modulation can include inhibition of lymphocyte proliferation, inhibition of lymphocyte trafficking and homing to the small bowel, and inhibition of the anti-inflammatory response (Table 4). CCX282-B is an

Table 4 Phase 2 studies exploring lymphocyte trafficking and homing inhibitors

NCT number	Study title	Study status (Completion date)	Drug	Mechanism	Primary outcome measures	Sponsor	Phases
NCT00540657	A Phase 2 study of CCX282-B in patients with CD	Completed (July 2008)	CCX282 *vs* placebo	CCX282-B is a chemokine receptor CCR9 antagonist that regulates migration and activation of inflammatory cells in the intestine	Evaluation of the effect of CCX282-B compared to placebo on the Vh:Cd ratio of small intestinal biopsy specimens taken from patients with CD, before and after gluten exposure	ChemoCentryx	Phase 2
NCT02929316	Vedolizumab induction may prevent celiac enteritis	Terminated (October 5, 2018)	Vedolizumab	Vedolizumab is a monoclonal antibody against integrin α4β7 that inhibit lymphocyte homing to the bowel	Histopathologic remission following induction with vedolizumab (defined as negative CD antibodies and normal duodenal biopsies) at 12 weeks	AGA Clinical Research Associates, LLC	Phase 2
NCT04806737	A Phase 2a, double-blind, randomized, placebo-controlled study on the efficacy and tolerability of a 14-day treatment with teriflunomide *vs* placebo in subjects with coeliac disease undergoing a 3-day gluten challenge	Unknown (August 15, 2022)	Oral teriflunomide *vs* placebo	Teriflunomide inhibits *de novo* synthesis of pyrimidine, performing a cytostatic effect on lymphocyte proliferation	Check the adaptive T-cell activation, evaluating the expression of CD38 on HLA-DQ: Gluten tetramer-positive T cells on peripheral blood on day 4 after a 3-day gluten challenge	Oslo University Hospital	Phase 1-phase 2
NCT02637141	A Phase 2a, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of AMG 714 in adult patients with CD	Completed (May 2, 2017)	AMG 714 *vs* placebo	AMG 714 is a monoclonal antibody an anti-IL-15, a pivotal cytokine in CD pathogenesis	Percent change from baseline in Vh:CD. To evaluate the attenuation of the effects of gluten exposure after 10 weeks of gluten challenge at week 12	Amgen	Phase 2
NCT02633020	A Phase 2a, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of AMG 714 in adult patients with type II refractory CD	Completed (May 2, 2017)	AMG 714 *vs* placebo	AMG 714 is a monoclonal antibody anti-IL-15	Percent change from baseline in the percentage of aberrant intestinal intraepithelial lymphocytes with respect to all intraepithelial lymphocytes at baseline and week 12	Amgen	Phase 2
NCT04424927 proactive	A Phase 2b, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of PRV-015 in adult patients with non-responsive CD as an adjunct to a gluten-free diet	Recruiting (August 31, 2024)	PRV-015 *vs* placebo	PRV-015 is a monoclonal antibody against IL-15, a pivotal cytokine in CD pathogenesis	Efficacy of PRV-015 in attenuating the symptoms of CD in non-responsive CD as measured by the celiac disease patient-reported outcome questionnaire at 24 weeks	Provention Bio, Inc.	Phase 2
NCT05636293	Double-blind, placebo-controlled trial to establish safety and efficacy of ritlecitinib to prevent gluten-induced celiac enteropathy and symptoms in CD patients in remission	Recruiting (January 1, 2025)	Ritlecitinib *vs* placebo	Ritlecitinib is a selective Janus kinase 3 inhibitors that prevent lymphocyte activation and proliferation	Change in small intestinal histology based on Vh:Cd ratio to characterize the gluten-challenge induced changes. Patient-reported outcomes defined as CD PRO to evaluate gluten challenge-triggered symptoms. Through study completion, average of 1 year	Massachusetts General Hospital	Phase 2

CD: Celiac disease; CCR9: C-C chemokine receptor type 9; IL: Interleukin; PROs: Patient-reported outcomes; Vh:Cd: Villous height to crypt depth ratio.

orally administrated C-C chemokine receptor type 9 (CCR9) antagonist previously studied for the treatment of Crohn's disease, in which it generated contrasting results. CCR9 is expressed on circulating lymphocytes and is the key chemokine receptor determining intestinal homing[55,56]. The ligand of CCR9 is C-C chemokine ligand 25, which is expressed in the intestinal epithelium and is upregulated in the presence of inflammation[57]. A double-blind, randomized, placebo-controlled, Phase 2 study (NCT00540657) evaluated its effectiveness in mitigating the effects of gluten ingestion in patients with CD. Ninety patients were enrolled, and half of them were treated by CCX282-B 250 mg twice daily for 13 weeks. The primary outcome was the evaluation of the effect of CCX282-B compared to placebo on the Vh:Cd ratio of small intestinal biopsy specimens taken from subjects with CD, before and after gluten exposure. Secondary outcomes were the evaluation of small intestinal mucosal inflammation, celiac serology, and symptom scores. Although the study was completed in 2008, its results have never been published.

Another component necessary for the "gut-homing phenotype" is constituted by α4β7-integrin, belonging to a heterodimeric noncovalently bound transmembrane receptor family involved in cell-cell and cell-extracellular matrix interactions. This specific heterodimer is present in more than 90% of intestinal lymphocytes, and its main ligand is the mucosal addressin cell adhesion molecule, present in the gastrointestinal tract and associated lymphoid tissue[58,59]. For this reason, a Phase 2 study (NCT02929316) aimed at evaluating if vedolizumab, a well-known monoclonal antibody against integrin α4β7, approved for the treatment of ulcerative colitis and Crohn's disease, could prevent small bowel atrophy in patients with CD after gluten challenge. However, this study was stopped in October 2018, due to lack of enrollment. Another approach could be preventing lymphocyte proliferation, possibly focusing on intestinal ones reacting to gluten peptides. In 2021 a Phase 2a, double-blind, randomized, placebo-controlled study (NCT04806737) evaluated the efficacy and tolerability of a 14-day treatment with teriflunomide in 15 subjects with CD, undergoing a 3-day gluten challenge. Teriflunomide is an orally administrated drug currently approved for the treatment of multiple sclerosis. It inhibits *de novo* synthesis of pyrimidine, performing a cytostatic effect on lymphocyte proliferation[60]. Even in this case, results are not available.

Lymphocytes involved in the pathogenesis of CD can be prompted to induce intestinal damage through the production of different mediators, including cytokines. Among them, a pivotal role has been recognized for IL-15, which can act on several cell types, including intraepithelial lymphocytes. A double-blind, Phase 2a trial (NCT02637141) investigated the effect of AMG-714, an anti-IL-15 monoclonal antibody, in patients with CD undergoing gluten challenge. In this study, 64 patients were randomly assigned to 150 mg AMG 714, 300 mg AMG 714, or placebo, administered by two subcutaneous injections every 2 weeks for 10 weeks. Patients without severe villous atrophy at baseline received also a gluten challenge. Duodenal biopsies were done at baseline and at the end of the study, in order to evaluate change in Vh:Cd ratio as primary outcome. Secondary outcomes included intraepithelial lymphocyte density, improvement in Marsh-Oberhuber score, changes in anti-transglutaminase and anti-deaminated gliadin peptide antibodies, number of bowel movements, percentage of diarrhea and changes in Gastrointestinal Symptom Rating Scale Score and in total Celiac Disease Gastrointestinal Symptom Rating Scale, questionnaires used to assess symptoms as diarrhea, indigestion, constipation, abdominal pain and reflux. The study demonstrated that Vh:Cd ratio was not significantly different between the groups of patients. However, changes in lymphocyte density and in symptoms suggest that further research of AMG 714 may be warranted in patients with non-responsive CD[61].

In fact, due to these encouraging results, the NCT02633020 trial evaluated the efficacy and safety of AMG 714 in patients with type II refractory CD. In this study 28 refractory patients with CD were randomly assigned to 8 mg/kg AMG 714 or placebo intravenous infusion on day 0, day 7, and every 2 weeks for 10 weeks. The primary outcome was to evaluate the reduction from baseline of aberrant intestinal intraepithelial lymphocytes, measured by flow cytometry after small intestinal biopsy collection. According to the study, there was no difference between the groups in terms of the primary endpoint of aberrant intraepithelial lymphocyte reduction from baseline, but there was a reduction of the number of patients with diarrhea[62].

Another ongoing Phase 2b trial (NCT04424927) is evaluating the efficacy and safety in adult patients with non responder CD on a GFD of three-dose regimens of PRV-015, which is also a monoclonal antibody against IL-15. This study is expected to be completed in August 2024. The ongoing NCT05636293 trial aims to establish the safety and efficacy of ritlecitinib, a selective Janus kinase 3 (JAK3) inhibitor, to prevent gluten-induced enteropathy and symptoms in patients with CD. JAK is a family of non-receptor tyrosine kinases, which include, in mammals, JAK1, JAK2, JAK3, and tyrosine kinase 2. Each protein has a kinase domain and binds cytokine receptors through amino terminal domains. Upon binding of the ligand to cytokine receptors, JAKs are activated and phosphorylate the receptors, allowing the binding of the signal transducer and activator of transcription family members[63]. In addition to the inflammatory response, several studies have demonstrated that JAKs are essential for intestine differentiation and damage repair[64-66]. IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 depend on both JAK1 and JAK3 to elicit their intracellular effects, and JAK3 is expressed in immune cells as well as in intestinal epithelial cells. In the trial, participants are randomized to placebo or ritlecitinib 200 mg capsule once per day and are also taking 10 g gluten once per day, for a total of 21 days, decreasing to 5 g daily after day 3 of the study if not tolerated. The primary outcome is to evaluate changes in small bowel histology based on Vh:Cd ratio, while the secondary outcomes are focused on patient-reported outcomes. The study will finish in 2025.

Helminth infestation

According to the "hygiene hypothesis", a reduction in the incidence of infectious diseases, especially of the helminth ones, can be responsible for the increasing prevalence of allergic and autoimmune diseases. From this scenario, studies arose about the possibility of suppressing the immunopathology induced by gluten and restoring tolerance in CD-inoculating patients with hookworms. NCT00671138 was a prospective, randomized, double-blinded, placebo-controlled Phase 2 trial evaluating the safety, tolerability and immunological effects of *Necator Americanus* infection in subjects with CD in remission on GFD during gluten challenge. This trial enrolled 20 patients: 10 were inoculated with hookworm and

compared with the other 10 uninfected patients. Duodenal and rectal biopsies were performed before and after gluten challenge; blood samples were also collected at the same time. Mucosal damage, systemic inflammatory response, clinical response to gluten challenge, and mucosal inflammatory response did not differ between the two groups of patients before and after gluten challenge. So even if hookworm infection is safe, it was not able to mitigate the small bowel damage induced by gluten[67]. On the other hand, a subsequent Phase 2 study (NCT01661933) aiming to establish the influence of hookworm infection in preventing intestinal damage and symptoms using escalating gluten challenges, suggested that it could promote immune regulation, provoking tolerance to gluten in CD. A more recent randomized, placebo-controlled Phase 1 trial (NCT02754609) conducted on 54 patients concluded that hookworm infection does not restore tolerance to sustained moderate consumption of gluten, but it is associated with improved symptom scores after intermittent consumption of very low gluten doses[68]. However, considering the nature of the treatment it is difficult to imagine routine clinical use of hookworm infection in the management of CD.

PROGRESS IN PHASE 3 TRIALS

Larazotide acetate, a promising therapeutic agent for CD, has been the subject of extensive clinical research, culminating in its progression to Phase 3 trials. The Phase 3 trial of larazotide acetate (NCT03569007), also known as CedLara, represented a critical step in the drug's development and aimed to evaluate its efficacy and safety in alleviating symptoms in CD patients. Whereas larazotide resulted promising in Phase 2 trials in alleviating gluten-related symptoms in patients with CD adhering to a GFD, recent developments in the ongoing Phase 3 trial have posed significant challenges. An independent statistical analysis showed that a substantial increase in the number of participants was required to achieve scientifically meaningful results. The additional need for patients was deemed too great, so the company overseeing the trial, concluded that it was not feasible to continue the trial under these conditions.

DISCUSSION

The current landscape of CD treatment is on the cusp of a paradigm shift. For decades, CD has been treated primarily dietary, with a strict GFD at its core. Although the GFD is effective for many, it comes with significant challenges, including dietary restrictions, social and psychological distress, and the risk of accidental gluten exposure. Our review highlights the need for alternative therapeutic strategies that address these unmet needs in the treatment of CD (Figure 2). The development of non-dietary therapies, such as gluten sequestrants, transglutaminase inhibitors and lymphocyte trafficking inhibitors, represents a major advance. These new therapies offer the promise of reducing the burden of strict dietary adherence and improving the quality of life for CD patients. However, there are still some challenges. While Phase 2 studies are promising, the efficacy and safety profiles of these therapies in broader patient populations need to be further validated in Phase 3 studies. For instance, therapies such as larazotide acetate and ZED 1227 have shown the potential in mitigating gluten-induced symptoms and intestinal damage, but their long-term effects and side-effect profiles need to be studied more extensively. Moreover, CD is a heterogeneous disease and individual responses to these emerging therapies may vary. Personalized medicine approaches, potentially incorporating genetic, immunological and microbiological data, could play a critical role in optimizing treatment efficacy. As these therapies are tested in clinical trials, there is a need for confirmation in Phase 3 trials for their integration into clinical practice. This integration will likely require multidisciplinary collaboration, including gastroenterologists, dietitians and patient education specialists. In addition, the role of these therapies in specific patient groups, such as patients with refractory CD or those at high risk of complications, needs to be investigated.

The advent of new therapies also brings with it ethical and social considerations. The autonomy of patients and their right to choose between dietary or pharmacological treatment must be respected. However, the development of new pharmacological treatments is costly and it is important to consider that resources should be prioritized where there is a clinical need. While respecting patient autonomy in choosing between dietary or pharmacologic treatment, it is critical to balance these options with the economic impact and practicality of making advanced treatments available to all patients who can benefit from them. Looking forward, the field of CD treatment is ready for further discoveries and innovations. Future areas of research include the development of personalized treatment strategies, long-term safety studies of new drugs, and research into adjunctive therapies to improve quality of life. In addition, ongoing research into the pathophysiology of CD may reveal novel therapeutic targets.

CONCLUSION

The horizon of CD treatment is expanding beyond dietary treatment, giving hope for better outcomes for patients. However, the path from promising clinical trial results to practical, everyday treatments is complex and requires careful consideration of efficacy, safety, accessibility, and patient preference. Continued research, patient-centered care and collaborative clinical practice will be critical to making these emerging therapies a new standard in the treatment of CD.

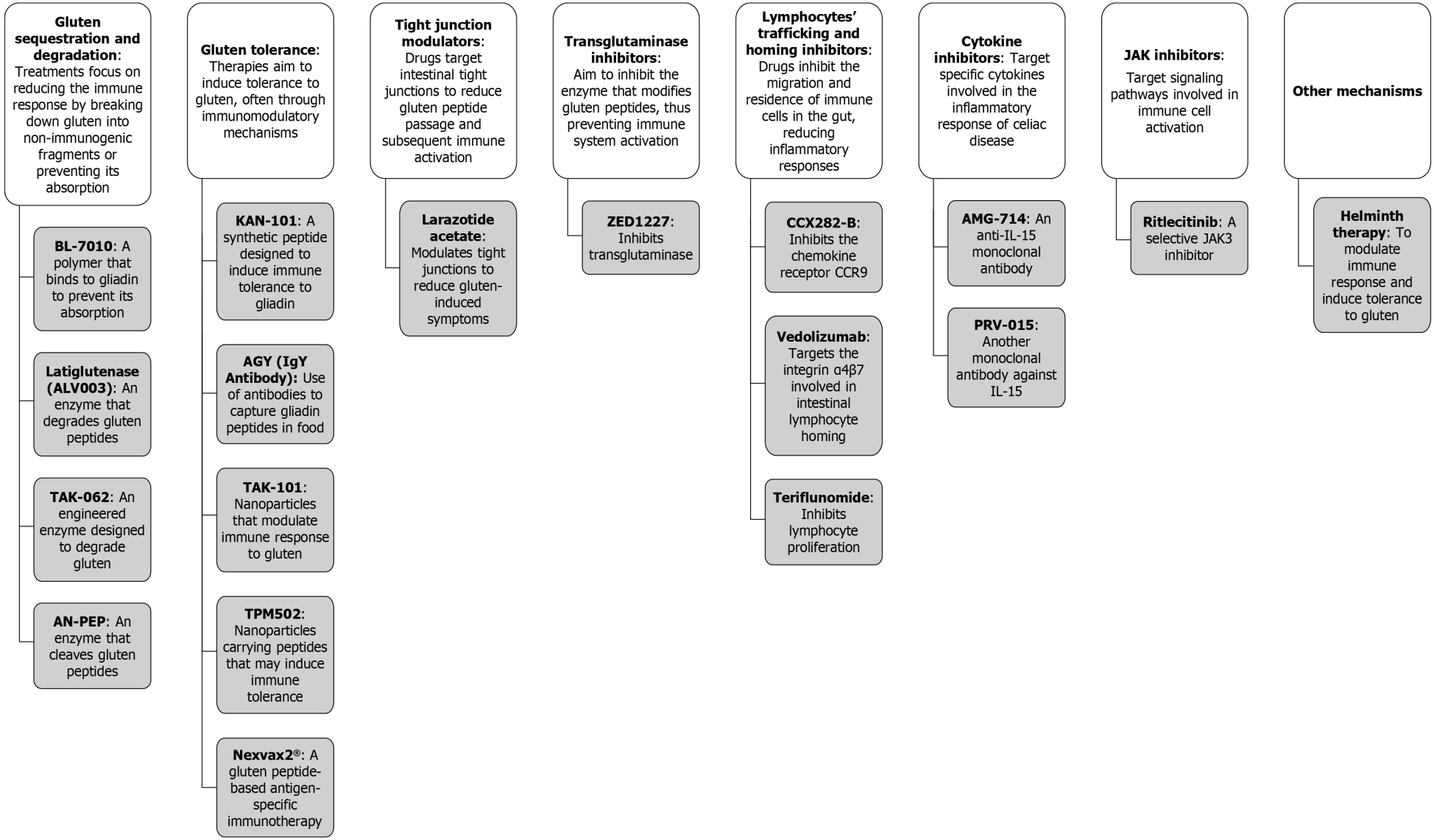

Figure 2 Emerging therapeutic strategies from Phase 2 trials in celiac disease treatment. CCR9: C-C chemokine receptor type 9; IL: Interleukin; JAK3: Janus kinase 3.

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REFERENCES

1 **Ludvigsson JF**, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C. The Oslo definitions for coeliac disease and related terms. *Gut* 2013; **62**: 43-52 [PMID: 22345659 DOI: 10.1136/gutjnl-2011-301346]

2 **King JA**, Jeong J, Underwood FE, Quan J, Panaccione N, Windsor JW, Coward S, deBruyn J, Ronksley PE, Shaheen AA, Quan H, Godley J, Veldhuyzen van Zanten S, Lebwohl B, Ng SC, Ludvigsson JF, Kaplan GG. Incidence of Celiac Disease Is Increasing Over Time: A Systematic Review and Meta-analysis. *Am J Gastroenterol* 2020; **115**: 507-525 [PMID: 32022718 DOI: 10.14309/ajg.0000000000000523]

3 **Singh P**, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, Kelly CP, Ahuja V, Makharia GK. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 823-836.e2 [PMID: 29551598 DOI: 10.1016/j.cgh.2017.06.037]

4 **Stamnaes J**, Sollid LM. Celiac disease: Autoimmunity in response to food antigen. *Semin Immunol* 2015; **27**: 343-352 [PMID: 26603490 DOI: 10.1016/j.smim.2015.11.001]

5 **Zarkadas M**, Cranney A, Case S, Molloy M, Switzer C, Graham ID, Butzner JD, Rashid M, Warren RE, Burrows V. The impact of a gluten-free diet on adults with coeliac disease: results of a national survey. *J Hum Nutr Diet* 2006; **19**: 41-49 [PMID: 16448474 DOI: 10.1111/j.1365-277X.2006.00659.x]

6 **Mouslih A**, El Rhazi K, Bahra N, Lakhdar Idrissi M, Hida M. Gluten-Free Diet Compliance in Children With Celiac Disease and Its Effect on Clinical Symptoms: A Retrospective Cohort Study. *Cureus* 2023; **15**: e50217 [PMID: 38077661 DOI: 10.7759/cureus.50217]

7 **Hall NJ**, Rubin G, Charnock A. Systematic review: adherence to a gluten-free diet in adult patients with coeliac disease. *Aliment Pharmacol Ther* 2009; **30**: 315-330 [PMID: 19485977 DOI: 10.1111/j.1365-2036.2009.04053.x]

8 **Silvester JA**, Comino I, Kelly CP, Sousa C, Duerksen DR; DOGGIE BAG Study Group. Most Patients With Celiac Disease on Gluten-Free Diets Consume Measurable Amounts of Gluten. *Gastroenterology* 2020; **158**: 1497-1499.e1 [PMID: 31866245 DOI: 10.1053/j.gastro.2019.12.016]

9 **Fernández-Bañares F**, Beltrán B, Salas A, Comino I, Ballester-Clau R, Ferrer C, Molina-Infante J, Rosinach M, Modolell I, Rodríguez-Moranta F, Arau B, Segura V, Fernández-Salazar L, Santolaria S, Esteve M, Sousa C; CADER study group. Persistent Villous Atrophy in De Novo Adult Patients With Celiac Disease and Strict Control of Gluten-Free Diet Adherence: A Multicenter Prospective Study (CADER Study). *Am J Gastroenterol* 2021; **116**: 1036-1043 [PMID: 33491958 DOI: 10.14309/ajg.0000000000001139]

10 **Syage JA**, Kelly CP, Dickason MA, Ramirez AC, Leon F, Dominguez R, Sealey-Voyksner JA. Determination of gluten consumption in celiac disease patients on a gluten-free diet. *Am J Clin Nutr* 2018; **107**: 201-207 [PMID: 29529159 DOI: 10.1093/ajcn/nqx049]

11 **Akobeng AK**, Thomas AG. Systematic review: tolerable amount of gluten for people with coeliac disease. *Aliment Pharmacol Ther* 2008; **27**: 1044-1052 [PMID: 18315587 DOI: 10.1111/j.1365-2036.2008.03669.x]

12 **Catassi C**, Fabiani E, Iacono G, D'Agate C, Francavilla R, Biagi F, Volta U, Accomando S, Picarelli A, De Vitis I, Pianelli G, Gesuita R, Carle F, Mandolesi A, Bearzi I, Fasano A. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. *Am J Clin Nutr* 2007; **85**: 160-166 [PMID: 17209192 DOI: 10.1093/ajcn/85.1.160]

13 **Kupper C**. Dietary guidelines and implementation for celiac disease. *Gastroenterology* 2005; **128**: S121-S127 [PMID: 15825119 DOI: 10.1053/j.gastro.2005.02.024]

14 **Gutowski ED**, Weiten D, Green KH, Rigaux LN, Bernstein CN, Graff LA, Walker JR, Duerksen DR, Silvester JA. Can individuals with celiac

disease identify gluten-free foods correctly? *Clin Nutr ESPEN* 2020; **36**: 82-90 [PMID: 32220373 DOI: 10.1016/j.clnesp.2020.01.012]
15 **Lee AR**, Wolf RL, Lebwohl B, Ciaccio EJ, Green PHR. Persistent Economic Burden of the Gluten Free Diet. *Nutrients* 2019; **11** [PMID: 30769836 DOI: 10.3390/nu11020399]
16 **Marciniak M**, Szymczak-Tomczak A, Mahadea D, Eder P, Dobrowolska A, Krela-Kaźmierczak I. Multidimensional Disadvantages of a Gluten-Free Diet in Celiac Disease: A Narrative Review. *Nutrients* 2021; **13** [PMID: 33669442 DOI: 10.3390/nu13020643]
17 **Diez-Sampedro A**, Olenick M, Maltseva T, Flowers M. A Gluten-Free Diet, Not an Appropriate Choice without a Medical Diagnosis. *J Nutr Metab* 2019; **2019**: 2438934 [PMID: 31354988 DOI: 10.1155/2019/2438934]
18 **Brera C**, Debegnach F, De Santis B, Di Ianni S, Gregori E, Neuhold S, Valitutti F. Exposure assessment to mycotoxins in gluten-free diet for celiac patients. *Food Chem Toxicol* 2014; **69**: 13-17 [PMID: 24694905 DOI: 10.1016/j.fct.2014.03.030]
19 **Raehsler SL**, Choung RS, Marietta EV, Murray JA. Accumulation of Heavy Metals in People on a Gluten-Free Diet. *Clin Gastroenterol Hepatol* 2018; **16**: 244-251 [PMID: 28223206 DOI: 10.1016/j.cgh.2017.01.034]
20 **Zingone F**, Swift GL, Card TR, Sanders DS, Ludvigsson JF, Bai JC. Psychological morbidity of celiac disease: A review of the literature. *United European Gastroenterol J* 2015; **3**: 136-145 [PMID: 25922673 DOI: 10.1177/2050640614560786]
21 **Shah S**, Akbari M, Vanga R, Kelly CP, Hansen J, Theethira T, Tariq S, Dennis M, Leffler DA. Patient perception of treatment burden is high in celiac disease compared with other common conditions. *Am J Gastroenterol* 2014; **109**: 1304-1311 [PMID: 24980880 DOI: 10.1038/ajg.2014.29]
22 **Gholmie Y**, Lee AR, Satherley RM, Schebendach J, Zybert P, Green PHR, Lebwohl B, Wolf R. Maladaptive Food Attitudes and Behaviors in Individuals with Celiac Disease and Their Association with Quality of Life. *Dig Dis Sci* 2023; **68**: 2899-2907 [PMID: 37024737 DOI: 10.1007/s10620-023-07912-6]
23 **Baggus EMR**, Hadjivassiliou M, Cross S, Penny H, Urwin H, Watson S, Woodward JM, Sanders DS. How to manage adult coeliac disease: perspective from the NHS England Rare Diseases Collaborative Network for Non-Responsive and Refractory Coeliac Disease. *Frontline Gastroenterol* 2020; **11**: 235-242 [PMID: 32419915 DOI: 10.1136/flgastro-2019-101191]
24 **Galli G**, Esposito G, Lahner E, Pilozzi E, Corleto VD, Di Giulio E, Aloe Spiriti MA, Annibale B. Histological recovery and gluten-free diet adherence: a prospective 1-year follow-up study of adult patients with coeliac disease. *Aliment Pharmacol Ther* 2014; **40**: 639-647 [PMID: 25066096 DOI: 10.1111/apt.12893]
25 **Rowinski SA**, Christensen E. Epidemiologic and therapeutic aspects of refractory coeliac disease - a systematic review. *Dan Med J* 2016; **63** [PMID: 27910801]
26 **Shan L**, Molberg Ø, Parrot I, Hausch F, Filiz F, Gray GM, Sollid LM, Khosla C. Structural basis for gluten intolerance in celiac sprue. *Science* 2002; **297**: 2275-2279 [PMID: 12351792 DOI: 10.1126/science.1074129]
27 **Goel G**, Tye-Din JA, Qiao SW, Russell AK, Mayassi T, Ciszewski C, Sarna VK, Wang S, Goldstein KE, Dzuris JL, Williams LJ, Xavier RJ, Lundin KEA, Jabri B, Sollid LM, Anderson RP. Cytokine release and gastrointestinal symptoms after gluten challenge in celiac disease. *Sci Adv* 2019; **5**: eaaw7756 [PMID: 31457091 DOI: 10.1126/sciadv.aaw7756]
28 **McCarville JL**, Nisemblat Y, Galipeau HJ, Jury J, Tabakman R, Cohen A, Naftali E, Neiman B, Halbfinger E, Murray JA, Anbazhagan AN, Dudeja PK, Varvak A, Leroux JC, Verdu EF. BL-7010 demonstrates specific binding to gliadin and reduces gluten-associated pathology in a chronic mouse model of gliadin sensitivity. *PLoS One* 2014; **9**: e109972 [PMID: 25365555 DOI: 10.1371/journal.pone.0109972]
29 **Pinier M**, Verdu EF, Nasser-Eddine M, David CS, Vézina A, Rivard N, Leroux JC. Polymeric binders suppress gliadin-induced toxicity in the intestinal epithelium. *Gastroenterology* 2009; **136**: 288-298 [PMID: 18992747 DOI: 10.1053/j.gastro.2008.09.016]
30 **Pinier M**, Fuhrmann G, Galipeau HJ, Rivard N, Murray JA, David CS, Drasarova H, Tuckova L, Leroux JC, Verdu EF. The copolymer P(HEMA-co-SS) binds gluten and reduces immune response in gluten-sensitized mice and human tissues. *Gastroenterology* 2012; **142**: 316-25.e1 [PMID: 22079593 DOI: 10.1053/j.gastro.2011.10.038]
31 **Gass J**, Vora H, Bethune MT, Gray GM, Khosla C. Effect of barley endoprotease EP-B2 on gluten digestion in the intact rat. *J Pharmacol Exp Ther* 2006; **318**: 1178-1186 [PMID: 16757540 DOI: 10.1124/jpet.106.104315]
32 **Gass J**, Bethune MT, Siegel M, Spencer A, Khosla C. Combination enzyme therapy for gastric digestion of dietary gluten in patients with celiac sprue. *Gastroenterology* 2007; **133**: 472-480 [PMID: 17681168 DOI: 10.1053/j.gastro.2007.05.028]
33 **Syage JA**, Murray JA, Green PHR, Khosla C. Latiglutenase Improves Symptoms in Seropositive Celiac Disease Patients While on a Gluten-Free Diet. *Dig Dis Sci* 2017; **62**: 2428-2432 [PMID: 28755266 DOI: 10.1007/s10620-017-4687-7]
34 **Lähdeaho ML**, Kaukinen K, Laurila K, Vuotikka P, Koivurova OP, Kärjä-Lahdensuu T, Marcantonio A, Adelman DC, Mäki M. Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease. *Gastroenterology* 2014; **146**: 1649-1658 [PMID: 24583059 DOI: 10.1053/j.gastro.2014.02.031]
35 **Murray JA**, Syage JA, Wu TT, Dickason MA, Ramos AG, Van Dyke C, Horwath I, Lavin PT, Mäki M, Hujoel I, Papadakis KA, Bledsoe AC, Khosla C, Sealey-Voyksner JA; CeliacShield Study Group. Latiglutenase Protects the Mucosa and Attenuates Symptom Severity in Patients With Celiac Disease Exposed to a Gluten Challenge. *Gastroenterology* 2022; **163**: 1510-1521.e6 [PMID: 35931103 DOI: 10.1053/j.gastro.2022.07.071]
36 **Pultz IS**, Hill M, Vitanza JM, Wolf C, Saaby L, Liu T, Winkle P, Leffler DA. Gluten Degradation, Pharmacokinetics, Safety, and Tolerability of TAK-062, an Engineered Enzyme to Treat Celiac Disease. *Gastroenterology* 2021; **161**: 81-93.e3 [PMID: 33741317 DOI: 10.1053/j.gastro.2021.03.019]
37 **Mitea C**, Havenaar R, Drijfhout JW, Edens L, Dekking L, Koning F. Efficient degradation of gluten by a prolyl endoprotease in a gastrointestinal model: implications for coeliac disease. *Gut* 2008; **57**: 25-32 [PMID: 17494108 DOI: 10.1136/gut.2006.111609]
38 **Montserrat V**, Bruins MJ, Edens L, Koning F. Influence of dietary components on Aspergillus niger prolyl endoprotease mediated gluten degradation. *Food Chem* 2015; **174**: 440-445 [PMID: 25529703 DOI: 10.1016/j.foodchem.2014.11.053]
39 **Salden BN**, Monserrat V, Troost FJ, Bruins MJ, Edens L, Bartholomé R, Haenen GR, Winkens B, Koning F, Masclee AA. Randomised clinical study: Aspergillus niger-derived enzyme digests gluten in the stomach of healthy volunteers. *Aliment Pharmacol Ther* 2015; **42**: 273-285 [PMID: 26040627 DOI: 10.1111/apt.13266]
40 **Tack GJ**, van de Water JM, Bruins MJ, Kooy-Winkelaar EM, van Bergen J, Bonnet P, Vreugdenhil AC, Korponay-Szabo I, Edens L, von Blomberg BM, Schreurs MW, Mulder CJ, Koning F. Consumption of gluten with gluten-degrading enzyme by celiac patients: a pilot-study. *World J Gastroenterol* 2013; **19**: 5837-5847 [PMID: 24124328 DOI: 10.3748/wjg.v19.i35.5837]
41 **Stefanolo JP**, Segura V, Grizzuti M, Heredia A, Comino I, Costa AF, Puebla R, Temprano MP, Niveloni SI, de Diego G, Oregui ME, Smecuol EG, de Marzi MC, Verdú EF, Sousa C, Bai JC. Effect of Aspergillus niger prolyl endopeptidase in patients with celiac disease on a long-term

gluten-free diet. *World J Gastroenterol* 2024; **30**: 1545-1555 [PMID: 38617446 DOI: 10.3748/wjg.v30.i11.1545]

42 **Janssen G**, Christis C, Kooy-Winkelaar Y, Edens L, Smith D, van Veelen P, Koning F. Ineffective degradation of immunogenic gluten epitopes by currently available digestive enzyme supplements. *PLoS One* 2015; **10**: e0128065 [PMID: 26030273 DOI: 10.1371/journal.pone.0128065]

43 **Murray JA**, Wassaf D, Dunn K, Arora S, Winkle P, Stacey H, Cooper S, Goldstein KE, Manchanda R, Kontos S, Grebe KM. Safety and tolerability of KAN-101, a liver-targeted immune tolerance therapy, in patients with coeliac disease (ACeD): a phase 1 trial. *Lancet Gastroenterol Hepatol* 2023; **8**: 735-747 [PMID: 37329900 DOI: 10.1016/S2468-1253(23)00107-3]

44 **Kelly CP**, Murray JA, Leffler DA, Getts DR, Bledsoe AC, Smithson G, First MR, Morris A, Boyne M, Elhofy A, Wu TT, Podojil JR, Miller SD; TAK-101 Study Group. TAK-101 Nanoparticles Induce Gluten-Specific Tolerance in Celiac Disease: A Randomized, Double-Blind, Placebo-Controlled Study. *Gastroenterology* 2021; **161**: 66-80.e8 [PMID: 33722583 DOI: 10.1053/j.gastro.2021.03.014]

45 **Goel G**, King T, Daveson AJ, Andrews JM, Krishnarajah J, Krause R, Brown GJE, Fogel R, Barish CF, Epstein R, Kinney TP, Miner PB Jr, Tye-Din JA, Girardin A, Taavela J, Popp A, Sidney J, Mäki M, Goldstein KE, Griffin PH, Wang S, Dzuris JL, Williams LJ, Sette A, Xavier RJ, Sollid LM, Jabri B, Anderson RP. Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: two randomised, double-blind, placebo-controlled phase 1 studies. *Lancet Gastroenterol Hepatol* 2017; **2**: 479-493 [PMID: 28506538 DOI: 10.1016/S2468-1253(17)30110-3]

46 **Gopalakrishnan S**, Durai M, Kitchens K, Tamiz AP, Somerville R, Ginski M, Paterson BM, Murray JA, Verdu EF, Alkan SS, Pandey NB. Larazotide acetate regulates epithelial tight junctions in vitro and in vivo. *Peptides* 2012; **35**: 86-94 [PMID: 22401908 DOI: 10.1016/j.peptides.2012.02.015]

47 **Mishra A**, Prakash S, Sreenivas V, Das TK, Ahuja V, Gupta SD, Makharia GK. Structural and Functional Changes in the Tight Junctions of Asymptomatic and Serology-negative First-degree Relatives of Patients With Celiac Disease. *J Clin Gastroenterol* 2016; **50**: 551-560 [PMID: 26535478 DOI: 10.1097/MCG.0000000000000436]

48 **DaFonte TM**, Valitutti F, Kenyon V, Locascio JJ, Montuori M, Francavilla R, Passaro T, Crocco M, Norsa L, Piemontese P, Baldassarre M, Fasano A, Leonard MM; CD-GEMM Study Group. Zonulin as a Biomarker for the Development of Celiac Disease. *Pediatrics* 2024; **153** [PMID: 38062791 DOI: 10.1542/peds.2023-063050]

49 **Jauregi-Miguel A**, Santin I, Garcia-Etxebarria K, Olazagoitia-Garmendia A, Romero-Garmendia I, Sebastian-delaCruz M, Irastorza I; Spanish Consortium for the Genetics of Celiac Disease, Castellanos-Rubio A, Bilbao JR. MAGI2 Gene Region and Celiac Disease. *Front Nutr* 2019; **6**: 187 [PMID: 31921880 DOI: 10.3389/fnut.2019.00187]

50 **Kelly CP**, Green PH, Murray JA, Dimarino A, Colatrella A, Leffler DA, Alexander T, Arsenescu R, Leon F, Jiang JG, Arterburn LA, Paterson BM, Fedorak RN; Larazotide Acetate Celiac Disease Study Group. Larazotide acetate in patients with coeliac disease undergoing a gluten challenge: a randomised placebo-controlled study. *Aliment Pharmacol Ther* 2013; **37**: 252-262 [PMID: 23163616 DOI: 10.1111/apt.12147]

51 **Leffler DA**, Kelly CP, Abdallah HZ, Colatrella AM, Harris LA, Leon F, Arterburn LA, Paterson BM, Lan ZH, Murray JA. A randomized, double-blind study of larazotide acetate to prevent the activation of celiac disease during gluten challenge. *Am J Gastroenterol* 2012; **107**: 1554-1562 [PMID: 22825365 DOI: 10.1038/ajg.2012.211]

52 **Leffler DA**, Kelly CP, Green PH, Fedorak RN, DiMarino A, Perrow W, Rasmussen H, Wang C, Bercik P, Bachir NM, Murray JA. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: a randomized controlled trial. *Gastroenterology* 2015; **148**: 1311-9.e6 [PMID: 25683116 DOI: 10.1053/j.gastro.2015.02.008]

53 **Schuppan D**, Mäki M, Lundin KEA, Isola J, Friesing-Sosnik T, Taavela J, Popp A, Koskenpato J, Langhorst J, Hovde Ø, Lähdeaho ML, Fusco S, Schumann M, Török HP, Kupcinskas J, Zopf Y, Lohse AW, Scheinin M, Kull K, Biedermann L, Byrnes V, Stallmach A, Jahnsen J, Zeitz J, Mohrbacher R, Greinwald R; CEC-3 Trial Group. A Randomized Trial of a Transglutaminase 2 Inhibitor for Celiac Disease. *N Engl J Med* 2021; **385**: 35-45 [PMID: 34192430 DOI: 10.1056/NEJMoa2032441]

54 **Isola J**, Mäki M, Hils M, Pasternack R, Viiri K, Dotsenko V, Montonen T, Zimmermann T, Mohrbacher R, Greinwald R, Schuppan D. The Oral Transglutaminase 2 Inhibitor ZED1227 Accumulates in the Villous Enterocytes in Celiac Disease Patients during Gluten Challenge and Drug Treatment. *Int J Mol Sci* 2023; **24** [PMID: 37445994 DOI: 10.3390/ijms241310815]

55 **Zabel BA**, Agace WW, Campbell JJ, Heath HM, Parent D, Roberts AI, Ebert EC, Kassam N, Qin S, Zovko M, LaRosa GJ, Yang LL, Soler D, Butcher EC, Ponath PD, Parker CM, Andrew DP. Human G protein-coupled receptor GPR-9-6/CC chemokine receptor 9 is selectively expressed on intestinal homing T lymphocytes, mucosal lymphocytes, and thymocytes and is required for thymus-expressed chemokine-mediated chemotaxis. *J Exp Med* 1999; **190**: 1241-1256 [PMID: 10544196 DOI: 10.1084/jem.190.9.1241]

56 **Pabst O**, Ohl L, Wendland M, Wurbel MA, Kremmer E, Malissen B, Förster R. Chemokine receptor CCR9 contributes to the localization of plasma cells to the small intestine. *J Exp Med* 2004; **199**: 411-416 [PMID: 14744993 DOI: 10.1084/jem.20030996]

57 **Papadakis KA**, Prehn J, Moreno ST, Cheng L, Kouroumalis EA, Deem R, Breaverman T, Ponath PD, Andrew DP, Green PH, Hodge MR, Binder SW, Targan SR. CCR9-positive lymphocytes and thymus-expressed chemokine distinguish small bowel from colonic Crohn's disease. *Gastroenterology* 2001; **121**: 246-254 [PMID: 11487533 DOI: 10.1053/gast.2001.27154]

58 **Erle DJ**, Briskin MJ, Butcher EC, Garcia-Pardo A, Lazarovits AI, Tidswell M. Expression and function of the MAdCAM-1 receptor, integrin alpha 4 beta 7, on human leukocytes. *J Immunol* 1994; **153**: 517-528 [PMID: 7517418]

59 **Briskin M**, Winsor-Hines D, Shyjan A, Cochran N, Bloom S, Wilson J, McEvoy LM, Butcher EC, Kassam N, Mackay CR, Newman W, Ringler DJ. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol* 1997; **151**: 97-110 [PMID: 9212736]

60 **Chong AS**, Huang W, Liu W, Luo J, Shen J, Xu W, Ma L, Blinder L, Xiao F, Xu X, Clardy C, Foster P, Williams JA. In vivo activity of leflunomide: pharmacokinetic analyses and mechanism of immunosuppression. *Transplantation* 1999; **68**: 100-109 [PMID: 10428276 DOI: 10.1097/00007890-199907150-00020]

61 **Lähdeaho ML**, Scheinin M, Vuotikka P, Taavela J, Popp A, Laukkarinen J, Koffert J, Koivurova OP, Pesu M, Kivelä L, Lovró Z, Keisala J, Isola J, Parnes JR, Leon F, Mäki M. Safety and efficacy of AMG 714 in adults with coeliac disease exposed to gluten challenge: a phase 2a, randomised, double-blind, placebo-controlled study. *Lancet Gastroenterol Hepatol* 2019; **4**: 948-959 [PMID: 31494096 DOI: 10.1016/S2468-1253(19)30264-X]

62 **Cellier C**, Bouma G, van Gils T, Khater S, Malamut G, Crespo L, Collin P, Green PHR, Crowe SE, Tsuji W, Butz E, Cerf-Bensussan N, Macintyre E, Parnes JR, Leon F, Hermine O, Mulder CJ; RCD-II Study Group Investigators. Safety and efficacy of AMG 714 in patients with type 2 refractory coeliac disease: a phase 2a, randomised, double-blind, placebo-controlled, parallel-group study. *Lancet Gastroenterol Hepatol* 2019; **4**: 960-970 [PMID: 31494097 DOI: 10.1016/S2468-1253(19)30265-1]

63 **Kumar N**, Kuang L, Villa R, Kumar P, Mishra J. Mucosal Epithelial Jak Kinases in Health and Diseases. *Mediators Inflamm* 2021; **2021**:

6618924 [PMID: 33814980 DOI: 10.1155/2021/6618924]

64 **Mishra J**, Verma RK, Alpini G, Meng F, Kumar N. Role of Janus kinase 3 in mucosal differentiation and predisposition to colitis. *J Biol Chem* 2013; **288**: 31795-31806 [PMID: 24045942 DOI: 10.1074/jbc.M113.504126]

65 **Gonneaud A**, Turgeon N, Boisvert FM, Boudreau F, Asselin C. JAK-STAT Pathway Inhibition Partially Restores Intestinal Homeostasis in Hdac1- and Hdac2-Intestinal Epithelial Cell-Deficient Mice. *Cells* 2021; **10** [PMID: 33498747 DOI: 10.3390/cells10020224]

66 **Herrera SC**, Bach EA. JAK/STAT signaling in stem cells and regeneration: from Drosophila to vertebrates. *Development* 2019; **146** [PMID: 30696713 DOI: 10.1242/dev.167643]

67 **Daveson AJ**, Jones DM, Gaze S, McSorley H, Clouston A, Pascoe A, Cooke S, Speare R, Macdonald GA, Anderson R, McCarthy JS, Loukas A, Croese J. Effect of hookworm infection on wheat challenge in celiac disease--a randomised double-blinded placebo controlled trial. *PLoS One* 2011; **6**: e17366 [PMID: 21408161 DOI: 10.1371/journal.pone.0017366]

68 **Croese J**, Miller GC, Marquart L, Llewellyn S, Gupta R, Becker L, Clouston AD, Welch C, Sidorenko J, Wallace L, Visscher PM, Remedios ML, McCarthy JS, O'Rourke P, Radford-Smith G, Loukas A, Norrie M, Masson JW, Gearry RB, Rahman T, Giacomin PR. Randomized, Placebo Controlled Trial of Experimental Hookworm Infection for Improving Gluten Tolerance in Celiac Disease. *Clin Transl Gastroenterol* 2020; **11**: e00274 [PMID: 33512796 DOI: 10.14309/ctg.0000000000000274]

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