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Novel Therapeutic Strategies for Celiac Disease

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ABSTRACT

Celiac disease (CeD) is a widespread autoimmune enteropathy caused by dietary gluten peptides in genetically susceptible individuals, which includes a range of intestinal and extraintestinal manifestations. Currently, there is no effective treatment for CeD other than strict adherence to a gluten-free diet (GFD). However, persistent or frequent symptoms and also partial villous atrophy were observed in some patients with CeD due to intentional or inadvertent gluten exposure during the use of GFD. It means that GFD alone is not enough to control CeD symptoms and long-term complications. Accordingly, new therapeutic approaches for CeD treatment such as gluten proteolysis, removing gluten from the digestive tract, promoting tight junction assembly, inhibiting intestinal tissue transglutaminase 2, using probiotics, and developing immunotherapeutic methods have been proposed through different strategies. This review focused on discussing the novel therapeutic strategies for CeD management.

KEYWORDS:

Celiac disease, Gluten, Auto-immune, Villous atrophy, Diet, Gluten-free, Therapy

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INTRODUCTION

Celiac disease (CeD), an autoimmune and chronic inflammatory condition of the small intestine that is caused by dietary gluten and related prolamins in genetically predisposed subjects, affects around 1% of the world population.¹⁻⁴ Gluten is a protein present in various cereals, including wheat, rye, and barley that can induce the intense innate and adaptive immune responses in some cases.^{5,6} Absorbent apparatus atrophy and nutrients malabsorption are the two main features of CeD.^{3,7} CeD manifestations vary from gastrointestinal (e.g., chronic and persistent diarrhea, abdominal pain, weight loss) to extra-intestinal (e.g., iron-deficiency anemia, osteoporosis, mouth ulcers, muscle weakness, fatigue) symptoms.^{8,9} Exact adherence to a gluten-free diet (GFD) is the only treatment of CeD. It means that patients should eliminate all gluten-containing foods from the diet throughout their life. It is difficult to follow GFD in some situations such as social events, eating outside the home, or for those with mental or psychological impairment.¹⁰⁻¹³ On the other hand, persistent or frequent symptoms and also partial



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villous atrophy were observed in some CeD cases despite dietary compliance; therefore, GFD is not a fully effective treatment for patients with CeD.^{14,15} There remains a need for finding new pharmaceuticals to protect against CeD and other gluten intolerance disorders and to make gluten ingestion safer for such patients.^{16,17} In recent years, due to the expansion in the understanding of CeD pathophysiology, several studies have focused on finding a novel therapeutic approach for this disease by using different strategies including gluten neutralization, mucosal gluten transportation disruption, antigen processing enzymes disruption, developing immunotherapeutic, using probiotics and numerous other approaches.^{16,18,19} This review focused on discussing the mentioned therapeutic approaches for CeD treatment.

Gluten neutralization

Latiglutenase

Gluten is known as the causative agent in CeD and is resistant to enzymatic proteolysis due to its high proline and glutamine residues. The entry of these undigested peptides into the lamina propria of the intestine is a trigger for the CeD pathogenesis.^{3,20,21}

Latiglutenase (ALV003), which is a mixture of barley cysteine endoprotease B, isoform 2 (EP-B2), and *Sphingomonas capsulata* prolyl endopeptidase (PEP) that proteolyze gluten at glutamine and proline residues, respectively, has an important role in diminishing the immunogenic potential of gluten-derived peptides.^{22,23} This enzyme can be used as an oral enzyme supplementation therapy for patients with CeD to aid in the digestion of dietary gluten peptides in the stomach before immunological response formation.¹⁹ Lähdeaho and colleagues²⁴ in 2014 performed a 6-week randomized, placebo-controlled study by comparing duodenal biopsy samples of proven CeD patients at baseline and after using latiglutenase or placebo together with the optimal daily dose (up to 2 g)¹ of gluten challenge. They reported that this glutenase could attenuate gluten-induced mucosal damages in CeD patients who were on a GFD with daily

consumption of gluten up to 2 g. They concluded that latiglutenase could be considered as a potential treatment for CeD. On the other hand, Murray and colleagues²⁵ in 2017 evaluated the effects of varying doses of latiglutenase on symptomatic CeD patients who had duodenal mucosal injury despite GFD for at least one year. The result of their study showed that latiglutenase did not have any improving effect on the patient's baseline histological and symptom scores when compared with placebo. Syage and co-workers,²⁶ in their double blind, placebo-controlled study in 2017 investigated the efficacy of 12-week latiglutenase treatment on seropositive and seronegative symptomatic CeD patients on a GFD for at least one year. They found that taking latiglutenase with meals caused symptomatic improvements in seropositive but not seronegative CeD patients, and this improvement was directly correlated with symptom severity. Syage and others believed that other etiologies such as, fructose and lactose intolerance, small intestinal bacterial overgrowth, microscopic colitis that are not related to gluten exposure could be the cause of CeD persistent symptoms. Therefore the lack of significant responses to a glutenase treatment in seronegative patients can be justified.²⁶ Syage and his co-workers,²³ in a similar study in 2019, reported that latiglutenase could improve the quality of life of patients with CeD. They also confirmed that latiglutenase was well tolerated by patients, as no serious adverse reactions after taking this enzyme were shown.

BL-7010

BL-7010 or P(HEMA-co-SS)², is a non-absorbable synthetic polymer with a high affinity for gluten-derived gliadin peptides. By binding to the gliadins, BL-7010 excretes these peptides from the digestive tract and protects them from enzymatic degradation. Therefore, BL-7010 significantly reduces the immunotoxicity of gliadins in the CeD patient's body.²⁷⁻²⁹

Pinier and others³⁰ in 2009 evaluated BL-7010 ability to diminish gliadin-induced intestinal changes and demonstrated that BL-7010 was effective in revoking gluten-associated toxic effects on cell permeability and

1. Gram

2. Poly (hydroxyethyl methacrylate-co-styrene sulfonate)

inflammation. Their group concluded that BL-7010 could successfully bind to gliadin and neutralize its pathological effects. In an ex-vivo study in 2012, the effects of the BL-7010-gliadin complex on cytokine releasing in intestinal biopsies of patients with CeD were measured.³¹ As a result, they reported that BL-7010 could reduce the secretion of TNF- α ³ in CeD intestinal samples.

Mucosal gluten transportation disruption Larazotide acetate

The intestinal epithelial tight junction (TJ) barrier is critical for controlling foreign particle entrance into the lamina propria.³² Untreated CeD patients have increased intestinal permeability resulting from abnormal expression of 'Zonulin', a tight junction reversible permeability regulator protein. Increased expression of zonulin leads to the augmented passage of gluten peptides into the lamina propria and autoimmune response formation in genetically predisposed individuals.^{3,27,33} Following the removal of gluten from the diet, the intestinal TJ's status improves partially.³⁴ However, intentional or inadvertent gluten exposure during GFD results in ongoing or persistent CeD symptoms.³⁵ It suggests that zonulin antagonist therapy can be used as a therapeutic option to improve CeD symptoms more than what is possible with the GFD alone.²⁷

Larazotide acetate (AT-1001) is a tight junction regulator derived from the *Vibrio cholerae* related toxin that can prevent the opening of intestinal TJs and reaching gluten to the intestinal submucosa. Thus, it prevents gliadin-induced inflammatory response formation and represents an important therapeutic option for CeD patients with persistent symptoms.^{19,36,37}

Kelly and colleagues³⁸ in their study in 2013, conducted an exploratory challenge with a daily intake of larazotide acetate or placebo and gluten for 6 weeks on patients with ≥ 6 months strict GFD. They evaluated the effect of larazotide acetate on intestinal permeability, tTG antibodies development,

and CeD symptoms in their subjects. The results of their study demonstrated that larazotide acetate could reduce CeD pathological manifestations after gluten exposure. Furthermore, Leffler and colleagues,³⁹ in their double-blind, placebo-controlled study in 2015, assessed the impact of larazotide acetate (0.5, 1, or 2 mg) on CeD patients with gastrointestinal symptoms despite a GFD for ≥ 12 months. They reported that 0.5 mg of larazotide acetate was the optimal dose that had a positive effect on reducing gastrointestinal (GI) and non-GI manifestations in this group of patients.

Antigen processing enzymes disruption

ZED1227

Upon entry of the partially digested gluten peptides into the lamina propria region, transglutaminase 2 (TG2) enzymes modify them to more immunotoxic deamidated form with high HLA⁴ affinity. This is the initial and crucial step of CeD pathogenesis.^{40,41} Therefore, TG2 inhibitors such as ZED1227 have shown great potential as a treatment for reducing CeD inflammatory responses.¹⁸

ZED1227 is an intestinal TG2 specific inhibitor that covalently binds to TG2 active site in patients with CeD and has high intestinal solubility and stability, which is in its initial phases of clinical trials.^{19,42} Encalada and co-workers⁴³ in their animal study in 2018 reported a decrease in TG2 enzyme activity to a normal state following the administration of ZED1227.

Immunotherapeutic

NexVax2

Nexvax2 is a novel gluten tolerizing vaccine candidate, which consists of three proprietary peptides, and aimed at restoring long-term tolerance to gluten for CeD patient's immune system, using the desensitization strategies of immunotherapy. Nexvax2 has been designed to protect patients with CeD against the inadvertent gluten consumption side effects by

3. Tumor necrosis factor- α

4. Human leukocyte antigen

Table 1: Summary of novel CeD therapeutic methods

Agent	Definition	
Gluten neutralizer	Latiglutenase	Proteolyze gluten at glutamine and proline residues.
	BL-7010	Sequester gliadins in the small intestinal lumen.
Gluten transportation disruptor	Larazotide acetate	Zonulin antagonist and tight junction agonist.
Antigen processing enzymes disruptor	ZED1227	TG2 inhibitor by covalently binding to its active sites.
Immunotherapeutic	NexVax2	Restore gluten tolerance of the patient's immune system by reprogramming the gluten responsive T-cells.
	Nanoparticle	Targeted delivery and inducing the immune response through different ways.
	HLA-DQ2/ DQ8 blocker	Block gliadin-binding sites on HLA-DQ2/ DQ8 alleles and prevent immune activation.
Refractory celiac disease therapeutic approaches	Budesonide	Suppress the immune system as a locally active steroid.
	IL-15 blocker	Prevent IL-15 signaling.
	TNF- α blocker	Prevent TNF- α inflammatory effects.
	Combination therapy	The combination of azathioprine with different drugs has been used to improve the condition of RCD patients.
Probiotics	Bifidobacterium lactis, VSL#3	Ameliorate intestinal dysbiosis and digest gluten peptides.

reprogramming the gluten responsive T-cells and help patients recover their normal diet and quality of life.^{44,45}

Daveson and others⁴⁶ in their study in 2017, assessed the safety and tolerability of the different doses of Nexvax2 on CeD patients who were on a GFD. They demonstrated that high-dose administration of Nexvax2 preceded by gradually increased dose levels was not accompanied by an increase in adverse events or inflammatory cytokine levels. They supported the Nexvax2 protection against dietary gluten. Additionally, Goel and others⁴⁷ also evaluated adverse events and safety of repeating Nexvax2 administrations on CeD patients compliant with GFD in 2017 and concluded that Nexvax2 therapy did not have any undesirable immune responses during treatment.

Nanoparticle

Nanoparticle (NP)-based drugs are known as the most effective factors on the GI tract, which can be synthesized in different sizes and perform diverse functions to provide the most powerful treatment for GI disorders.^{48,49} Attarwala and colleagues⁵⁰ in their study showed that gelatin nanoparticles containing small interfering RNA (siRNA) with the ability to silence the TG2 or IL-15 gene had an appropriate therapeutic capability in an in vitro model of CeD.⁵⁰ He and his colleagues, in their next

study, found that these nanoparticles, which were encapsulated within microspheres, could efficiently facilitate oral intestinal delivery of siRNA and had the potential to be used to combat CeD.⁵¹

TIMPs⁵ are negatively charged synthetic nanoparticles with intravenous injection capability that can induce immune tolerance to peptide and protein antigens through interaction with MARCO+ macrophages.^{52,53} Gliadin containing TIMPs (TIMP-GLIA) proposes to introduce gliadin peptide epitopes to CeD patients' immune systems in a tolerogenic manner. Freitag and co-workers,⁵⁴ in their recent study, reported that intravenous administration of TIMP-GLIA in gliadin sensitive murine models could restore peripheral tolerance to gluten.⁵⁴ Phase 1 and 2 of human clinical trials for this nanoparticle is currently underway with promising results.⁵⁴

HLA-DQ2 or HLA-DQ8 blocking

HLA class II genes (DQ2 or DQ8) are positively charged pockets and have a tendency to interact with deamidated gliadin peptides. HLA DQ2/8 plays a role in presenting gliadin peptides to gliadin specific CD4+ T cells and are considered as predisposing genetic factors for CeD.^{3,55} Therefore, HLA DQ2/ DQ8 blocking can be a potential strategy for

5. Tolerogenic Immune-Modifying nanoParticles

diminishing the toxic effects induced by gliadin in CeD patients.⁵⁶ Several DQ2/ DQ8 blocking peptide analogs have been designed to block gliadin binding sites on these alleles and prevent immune activation. This novel therapy is in its preclinical phase, and there is not enough available information about the efficacy and safety of these blockers.^{18,19,56}

Refractory celiac disease therapeutic approaches

A subgroup of CeD patients who have severe GI symptoms (despite 6-12 months on a GFD) and abnormal small bowel histopathology are categorized as refractory CeD (RCD). RCD is divided into two subtypes RCD I and II. RCD II can be an early stage of enteropathy-associated T-cell lymphoma (EATL).⁵⁷⁻⁵⁹ Strict gluten exclusion from the diet and administration of corticosteroids, either alone or in combination with other immunosuppressive drugs, are common therapeutic methods for RCD.^{60,61} As different results have been reported about the extent of corticosteroid responses in RCD patients, and this group of drugs has some systemic adverse effects, studies have focused on finding new appropriate therapy for RCD.⁶²

Glucocorticoid therapy

Budesonide is a glucocorticoid with poor oral bioavailability and local functions that has pharmacological effects on the gut mucosa and less harmful effects than other corticosteroids.⁴⁵ Daum and colleagues⁶⁰ in 2006 analyzed the efficacy and toxicity of budesonide in the treatment of RCD patients and found that budesonide could act as an effective therapeutic option for patients with RCD type I. Brar and co-workers⁶¹ in another study in 2007 assessed budesonide effects on patients with RCD type I and II and confirmed the role of budesonide in the control of refractory CeD.

IL- 15 blocking

Interleukin-15 (IL-15) is a potent pro-inflammatory cytokine with the ability to disrupt intestinal immune homeostasis and mediate the inflammatory response and has overexpression in the intestinal mucosa of the CeD patients.^{63,64} The degree of its intestinal

upregulation is directly related to the intensity of CeD mucosal damage and villous atrophy and is supposed to have a critical role in the refractory CeD expansion (especially type II).⁶⁵⁻⁶⁷ Thus, IL-15 is considered as an attractive target to achieve RCD suppression approach.⁶⁸

Humanized Mik-Beta-1⁶ is a monoclonal antibody that is capable of suppressing IL-15 action by saturating the IL-2/IL-15R β subunit (also known as IL2R β , CD122) and inhibiting the production of IL-2 or IL-15 stimulated cytokines.⁶⁹ Mik-Beta-1 is in phase 1 clinical trials for the treatment of refractory CeD.^{19,27} Moreover, Vicari and colleagues⁷⁰ in 2017 discovered a new anti-IL-15 monoclonal antibody, called CALY-002 that can prevent IL-15R $\beta\gamma$ complex signaling and has potential therapeutic use in the treatment of RCD.

TNF blocking

As TNF- α is a potent pro-inflammatory protein with the ability to induce intestinal inflammation, different studies have focused on evaluating the effectiveness of anti-TNF α antibodies such as infliximab in the treatment of RCD patients.⁷¹ The results of studies indicate the ability of infliximab to ameliorate histological damages, especially in patients with RCD I. Costantino and others,⁷² reported that long-term treatment of patients with RCD I with infliximab could progressively return the small intestinal condition of these patients to near normal. Gillett and colleagues,⁷³ in their report about a 47-year-old white woman with RCD, found that infliximab might be an effective treatment for patients with refractory CeD. However, there is a need for long-term data for establishing the safety and utility of this therapeutic method before wider use.⁷³

Combination therapy

Azathioprine is another immunosuppressive agent with the ability to inhibit the clonal expansion of B- and cytotoxic T-lymphocytes that is reported to be effective in RCD treatment, especially when steroids fail. Few studies have examined the effect of

6. A murine monoclonal antibody directed against the beta subunit of the interleukin-2 receptor

azathioprine on improving the condition of RCD patients, and the results are more promising regarding the RCD I.⁵⁹ In different cases, the combination of azathioprine with diverse drugs has been used. Sebastian Lasa reported the positive effect of combination therapy with budesonide and azathioprine on a 54-year-old man with RCD I.⁷⁴ It can also complement the action of prednisone, as Goerres and others⁷⁵ reported the appropriate efficacy of the combination of azathioprine and prednisolone for 1 year to achieve remission in patients with RCD I. However, it was not effective for patients with RCD II.⁷⁵ There is still a need for further studies with more patients for this type of treatment to get a definite conclusion.

Probiotics

Several studies worldwide reported intestinal microbiota dysbiosis in patients with CeD, which can hurt their health condition.⁷⁶ Moreover, there are some probiotics with the ability to ameliorate intestinal dysbiosis and digest gluten peptides.^{76,77} Therefore, there is a rising interest in the use of probiotics for CeD treatment.⁷⁸

Lindfors and colleagues⁷⁹ investigated the ability of *Lactobacillus fermentum* and *Bifidobacterium lactis* to reduce the toxic effects of gliadin peptides on Caco-2 cell line in 2008. They reported that *Bifidobacterium lactis* could counteract the harmful effects of gliadin polypeptides on epithelial cells. VSL#3 is a probiotic cocktail encompassing eight bacterial species (*Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus plantarum*, *L. acidophilus*, *L. casei*, *L. delbrueckii subsp. bulgaricus*, and *Streptococcus thermophilus*).⁸⁰ De Angelis and co-workers⁸¹ designed a study to evaluate VSL#3 capacity to hydrolyze wheat flour allergens into less immunogenic peptides in 2007. The result of this study supported the role of VSL#3 in effectively hydrolyzing gliadin polypeptides compared with other probiotics.

CONCLUSION

Currently, the mainstay of treatment for patients with CeD is complete adherence to a dietary regimen without gluten-containing foods. However, following a GFD

requires comprehensive education for paying careful attention to food selections and is not a simple task, especially at social events, eating outside the home, or for those with a mental or psychological impairment. This adds to the disease burden. However, while most CeD patients respond to the GFD, some patients continue to develop CeD symptoms and/or pathological abnormalities despite dietary compliance. Currently, by increasing the prevalence of this disease, there is a need to find complementary or alternative, non-dietary pharmaceuticals to control symptoms that are not controlled by the GFD alone. Several novel therapeutic approaches are ongoing or underway for CeD. In the present study, we have summarized a number of these CeD emerging therapies. It is noteworthy to mention that all of these treatments are investigative, and further studies on their efficacy and safety are still needed for decisively introducing one of them as a CeD non-dietary treatment.

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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