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MODULATING GLUTEN-TRIGGERED IMMUNITY: THE NEXT STEP IN CELIAC DISEASE TREATMENT

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ABSTRACT

Celiac disease (CeD) is an autoimmune condition triggered by gluten ingestion in genetically predisposed individuals. Although a strict gluten-free diet (GFD) remains the gold standard for treatment, many patients experience ongoing symptoms or fail to achieve mucosal healing due to inadvertent gluten exposure and challenges in long-term adherence. These limitations and growing understanding of the pathophysiology of CeD have prompted the development of non-dietary therapies that target the underlying immune mechanisms of CeD. Emerging therapeutic strategies aim to modulate gluten-triggered immunity, including the inhibition of tissue transglutaminase 2 (TG2), blockade of HLA-DQ2.5 and gluten peptide complexes, suppression of interleukin-15 (IL-15), and interference with gut-homing lymphocyte trafficking. Among these, the TG2 inhibitor ZED1227 has demonstrated the most advanced clinical efficacy, while IL-15–targeting agents such as AMG 714 and CALY-002 show promise, particularly in refractory CeD. However, to date, none of those novel immune-modulating strategies have yet demonstrated sufficient efficacy and safety to replace dietary therapy. Therefore, future well-designed, long-term studies are needed to validate the efficacy, safety, and cost-effectiveness of immune-mediated therapies and to define their role in personalized management of CeD.

KEYWORDS

Celiac Disease, Therapeutics, Gluten, Transglutaminase, Immunotherapy, Immune Tolerance

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1. Introduction

Celiac disease (CeD) is an autoimmune disorder that arises in genetically susceptible individuals following the consumption of gluten-containing foods. The global prevalence of CeD is estimated at around 0.7% based on histological findings, increasing to approximately 1.4% when assessed using serological markers (Singh et al., 2018). To date, strict and lifelong adherence to a gluten-free diet (GFD) remains the gold standard for the treatment of CeD. However, adherence rates in adult patients remain unsatisfactory, ranging from 42% to 91%, due to the ubiquitous presence of gluten, the high risk of cross-contamination, considerable social and psychological burdens, and limited access to reliably safe gluten-free products (Hall et al., 2009; Jamieson & Blewett, 2025; Schiepatti et al., 2022). Moreover, between 36% and 55% of patients who report strict adherence to a GFD do not achieve histological remission, likely due to unintentional gluten exposure (Barratt et al., 2011). Assessing adherence is further complicated by the lack of a single, widely accepted biomarker and the need to rely on self-reported data and dietary questionnaires, both of which are prone to bias and variability. These challenges have fueled growing interest in the underlying pathophysiology of CeD, particularly the mechanisms driving chronic inflammation and villous atrophy, with the goal of identifying new therapeutic targets that extend beyond dietary restriction. The aim of this review is to highlight the current challenges in CeD management and discuss novel, potential treatment strategies with a focus on therapeutics that target the immune response of patients with CeD after gluten exposure.

2. Methodology

We conducted a narrative review based on a comprehensive literature search. Scientific databases, including PubMed, Google Scholar, and Scopus, were used to identify relevant publications. Search terms such as "celiac disease", "therapeutics", "gluten", "transglutaminase", "immunotherapy", and "immune tolerance" were used in various combinations. Preference was given to peer-reviewed studies, systematic reviews, and meta-analyses published within the past 10–15 years, although older works were also considered when appropriate.

3. Pathophysiology of celiac disease

The pathogenesis of CeD is complex and characterized by a multi-step cascade triggered by gluten ingestion, which leads to immune-mediated mucosal damage. Key elements include genetic predisposition, epithelial barrier dysfunction, deamidation by tissue transglutaminase 2 (TG2), human leukocyte antigen (HLA)-restricted T-cell responses, and interleukin-15 (IL-15)– driven cytotoxicity. Gliadins, one of the two primary protein fractions found in wheat gluten, contain repetitive sequences rich in proline and glutamine. A feature that makes them resistant to complete degradation by gastrointestinal enzymes. This incomplete digestion allows immunogenic peptide fragments to persist in the small intestine and cross the intestinal epithelial barrier. Then, they undergo deamidation by the enzyme TG2, a step which is crucial for their increased affinity for HLA-DQ2 or HLA-DQ8 molecules present in individuals predisposed to the development of CeD. Once bound, these peptides are presented to CD4+ T cells in the lamina propria, initiating an adaptive immune response. Activated T cells release proinflammatory cytokines, including interferon-γ, interleukin-2, IL-21, and tumor necrosis factor-alpha (TNF-α), which contribute to mucosal damage (De Re et al., 2017; Patt et al., 2023). Moreover, this process is amplified by lymphocyte trafficking - selective recruitment of activated T cells to the intestinal mucosa. Gluten-reactive T cells upregulate gut-homing receptors, particularly integrin α4β7 and CCR9, which mediate migration of the T cells to the small intestine. In parallel, IL-15 plays a crucial role in activating intraepithelial lymphocytes (IELs), particularly cytotoxic CD8+ T cells, which directly contribute to the apoptosis of epithelial cells (Meresse et al., 2015). The combined effect of these innate and adaptive immune mechanisms leads to villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytosis. Notably, this heightened immune sensitivity to minimal amounts of gluten highlights the clinical challenge of achieving complete mucosal recovery solely through diet.

4. Gluten-free diet adherence evaluation

Despite reporting strict adherence to a GFD, many individuals with CeD remain at risk of ongoing intestinal injury due to inadvertent gluten consumption. Trace amounts of gluten—often hidden in processed foods or introduced through cross-contamination—may be sufficient to sustain mucosal inflammation and prevent histological recovery. According to current American College of Gastroenterology guidelines, assessment of dietary adherence should involve consultation with a dietitian experienced in GFD management (Rubio-Tapia et al., 2023). However, standard tools, such as structured questionnaires (e.g., the Biagi questionnaire), are subjective and rely on patient self-reporting, which may underestimate actual gluten intake or fail to capture accidental transgressions (Rodrigo et al., 2018). To improve the accuracy of adherence monitoring, alternative strategies have been explored. Serial measurement of celiac-specific antibody titers, while helpful in detecting significant dietary lapses, lacks the sensitivity to detect low-level exposure and is ineffective in older patients or those presenting with seronegative CeD (Ciccocioppo et al., 2015). Histologic evaluation via duodenal biopsy remains the most definitive method for assessing mucosal healing. However, it is invasive, costly, and poorly tolerated, particularly in asymptomatic patients (Rodrigo et al., 2018). As a less invasive alternative, detection of gluten immunogenic peptides (GIPs) in stool or urine has been proposed. These peptides, which resist gastrointestinal digestion and elicit strong immunologic responses in CeD, can be identified with high specificity and sensitivity, 100% and 98.5% respectively, shortly after gluten ingestion (Cenni et al., 2025; Comino et al., 2016; Moreno et al., 2017). However, currently available guidelines highlight that while GIP testing may confirm exposure, it does not reliably distinguish between clinically relevant and irrelevant amounts of gluten, and thus is not yet recommended for routine monitoring (Rubio-Tapia et al., 2023).

Given the limitations of current methods to accurately assess long-term dietary adherence and the considerable burden placed on patients to avoid even small amounts of gluten, there is a growing need for therapeutic approaches that directly modulate the immune response to gluten. Such interventions could improve patients' quality of life and reduce the ongoing risk of intestinal damage, representing a crucial advancement in the comprehensive management of CeD.

5. Transglutaminase inhibitors

TG2 plays a key role in the pathogenesis of CeD by deamidating gluten peptides, thereby increasing their affinity for HLA-DQ2 or HLA-DQ8 molecules and facilitating their presentation to CD4+ T cells (De Re et al., 2017). This, in turn, leads to the T-cell activation and the release of proinflammatory cytokines (Bodd et al., 2010). Therefore, in recent years, there has been a growing research interest in developing drugs that could inhibit the activity of TG2. Schuppan et al. studied the effectiveness of orally administered TG2 inhibitor ZED1227 in a phase 2, randomized, double-blind, placebo-controlled, 6-week trial (Schuppan et al., 2021). In this study, 160 adult patients with biopsy-confirmed CeD in clinical remission on a GFD were randomized to receive one of three daily doses of ZED1227 (10 mg, 50 mg, or 100 mg) or placebo. All participants underwent a controlled gluten challenge of 3 grams per day. The primary endpoint of the trial was the change in the villus height to crypt depth (VH:CrD) ratio, a histologic marker of mucosal injury. All three ZED1227 dose groups showed statistically significant attenuation of gluten-induced histologic damage compared to placebo, with the 50 mg and 100 mg doses yielding the most pronounced effects. Secondary endpoints included IEL counts, symptom scores, and safety outcomes. Although improvements in patient-reported outcomes were observed, they were not statistically significant, likely due to the short duration of the trial and relatively small sample size. Notably, the safety profile of ZED1227 was comparable to that of the placebo, with no serious drug-related adverse events.

A more recent study by Dotsenko et al. provided molecular confirmation of ZED1227's efficacy (Dotsenko et al., 2024). Transcriptomic analysis of duodenal biopsies obtained from patients with CeD has revealed that a daily dose of 100 mg ZED1227 effectively blocked nearly all gene expression changes associated with gluten exposure. These included key immune pathways, particularly those mediated by IFN-γ, which is known to amplify TG2 expression and promote the pathogenic cycle of gluten peptide deamidation. ZED1227 not only suppressed IFN-γ-related transcriptional activity but also reduced IEL infiltration and VH:CrD ratio. Importantly, this study also revealed that the degree of transcriptomic suppression varied depending on the HLA-DQ genotype. Patients homozygous for HLA-DQ2.5, a known risk factor for severe CeD, showed a weaker suppression of the IFNγ-driven inflammatory response, suggesting that higher doses or prolonged treatment may be required in this subgroup. These findings support a personalized medicine approach, with HLA genotyping serving as a potential tool for treatment stratification. In addition to clinical

and transcriptomic studies validating the efficacy of ZED1227, recent research has provided novel insights into the site of action of ZED1227 within the small intestinal mucosa. Isola et al. investigated the tissue distribution of orally administered ZED1227 by analyzing duodenal biopsies from patients with CeD during a controlled gluten challenge (Isola et al., 2023). Endoscopic duodenal samples were collected before treatment and after 24 hours from the last dose to compare drug localization and TG2 activity over time. Unexpectedly, ZED1227 localized primarily on the apical surface of villous enterocytes rather than in the lamina propria, where TG2 is most abundantly expressed. These findings suggest that pathogenic deamidation of gluten peptides may occur at the epithelial brush border, earlier than previously believed, which strengthens the hypothesis that epithelial TG2 plays a key role in initiating the gluten-driven immune cascade.

As maintaining and monitoring strict adherence to a GFD remains a challenge, available studies support the rationale to use ZED1227 as a targeted, well-tolerated adjunctive therapy capable of blocking gluten-induced intestinal damage at the earliest stages of CeD pathogenesis. However, future phase 3 clinical trials are crucial to confirm the long-term efficacy and safety of ZED1227, particularly under conditions of inadvertent gluten exposure. Moreover, investigations into optimal dosing regimens and treatment duration are also needed.

6. Antigen presentation blockade

Another promising direction in the development of non-dietary therapies for CeD involves disrupting the initial immune recognition of gluten peptides by selectively blocking HLA-DQ2.5 and gluten peptide complexes. DONQ52 is a monoclonal antibody that targets immunogenic gluten peptides presented by HLA-DQ2.5 (Okura et al., 2023). In a study conducted by Hardy et al., 44 patients with biopsy-confirmed CeD who had maintained strict adherence to a GFD for at least 12 months were challenged with wheat, barley, or rye over 3 days. Blood samples were collected prior to the challenge and again six days afterward to assess immune responses. Treatment with DONQ52, administered at concentrations of 4 or 40 μg/mL, led to a median reduction of 87% in wheat gluten-specific T-cell activation. T-cell responses to barley hordein and rye secalin were also significantly diminished. Importantly, DONQ52 showed no effect on T-cell responses to non-gluten antigens, indicating a high degree of selectivity (Hardy et al., 2024). These findings indicate that DONQ52 can selectively and effectively inhibit pathogenic T-cell responses in HLA-DQ2.5+ individuals, offering compelling preclinical support for its continued development as a targeted therapy for CeD. A first-in-human Phase 1 clinical trial (NCT05425446) is currently evaluating its safety and tolerability in patients with well-controlled CeD (*NCT05425446*, n.d.).

7. Targeting Immune Cell Migration

The selective migration of gluten-reactive lymphocytes to the small intestinal mucosa via α4β7 integrin and CCR9 chemokine receptor pathways has become another target in the development of non-dietary therapies for CeD. Several clinical trials have investigated whether disrupting this gut-homing mechanism could reduce intestinal inflammation and mucosal damage in affected individuals.

Vedolizumab, a monoclonal antibody targeting the α4β7 integrin, has been evaluated in a Phase 2 clinical trial (NCT02929316) in patients with biopsy-proven CeD who experience persistent symptoms and histologic damage despite adherence to a GFD (Kaufman, 2018). However, no efficacy results have been published yet, even though, according to ClinicalTrials.gov, the trial was terminated in October 2018.

Another promising agent, PTG-100, is an oral peptide antagonist of α4β7 integrin. A Phase 1b clinical trial (NCT04524221) completed in 2022 evaluated the safety and efficacy of PTG-100 in patients with CeD who underwent gluten challenge. While the concept of oral integrin blockade is attractive, especially in the light of a disease which requires lifelong management, no results have been published yet (Fernandez-Becker, 2022).

CCR9 is another therapeutic target in the management of CeD. A Phase 2 clinical trial (NCT00540657) aimed to determine if Vercirnon, an orally administered molecule capable of blocking the activity of the CCR9 chemokine receptor, can alleviate the effects of gluten exposure in patients with CeD (Amgen, 2025). However, despite this preliminary promise, the broader clinical development of Vercirnon was halted after subsequent phase III trials in Crohn's disease failed to meet primary endpoints (Staff, 2013).

Despite the strong pathophysiological rationale for targeting lymphocyte trafficking in CeD, clinical evidence supporting this strategy remains inconclusive. To date, no clinical trial has provided results supporting the efficacy of agents that block the α4β7 integrin and CCR9 chemokine receptor pathways.

8. IL-15 blockade

IL-15 plays a key role in the innate immune response, which contributes to the pathogenesis of CeD independently of gluten-specific adaptive responses. It drives the expansion and activation of cytotoxic IELs, particularly $CD8^+$ T-cells, which can destroy intestinal epithelial cells, leading to villus atrophy. What is more, IL-15 represents an especially attractive therapeutic target in cases of refractory celiac disease (RCD), a condition in which symptoms and villus atrophy persist for 12 months despite strict adherence to a GFD and the exclusion of any other causes of malabsorption (Elli et al., 2024; Hujoel & Murray, 2020). Lähdeaho et al. conducted the first Phase 2a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of repeated subcutaneous injections of AMG 714, an anti-IL-15 monoclonal antibody, in patients with CeD. After 12 weeks of follow-up, no statistically significant differences in VH:CrD ratio were observed, regardless of the dose (150 mg vs. placebo or 300 mg vs. placebo). However, the 300 mg dose appeared to alleviate gluten-induced effects, as indicated by reduced IEL counts, improvements in patient-reported symptoms, and a decrease in the incidence of diarrhea. Additionally, this dosage was well tolerated by the participants (Lähdeaho et al., 2019). A similar study, but in patients with RCD type 2, was performed by Cellier et al.. Participants with RCD type 2 were given 8 mg/kg of AMG 714 intravenously over 10-week period. The reduction of aberrant IELs count from baseline to week 12, the primary endpoint of the study, was not met. However, improvements in the IEL T-cell receptor clonality were accompanied by a reduction in the proportion of patients experiencing diarrhea, suggesting a potential symptomatic benefit of AMG 714 treatment (Cellier et al., 2019).

More recently, Vicari et al. evaluated CALY-002, a novel anti-IL-15 monoclonal antibody designed to neutralize both free and receptor-bound IL-15 with high potency. In a Phase 1a/b randomized, placebo-controlled trial (NCT04593251), patients with well-controlled CeD received increasing intravenous doses of CALY-002 while undergoing an 8-week gluten challenge. The treatment led to the attenuation of the gluten-induced mucosal deterioration, expressed by less pronounced reductions in the VH:CrD ratio and smaller increases in IEL counts compared to the placebo, particularly in the 700 mg cohort (Schumann et al., 2024). These findings support the potential of CALY-002 as an effective molecule to mitigate immune-mediated mucosal injury in CeD and justify further clinical research.

Currently, a new anti-IL-15 antibody, TEV-53408, is being tested in a Phase 1b clinical trial. The researchers aim to determine the safety and tolerance of a single injection of the drug in adults with CeD before and after eating snacks that contain gluten (*TEV-CeD2 Study*, n.d.).

Blocking IL-15 signaling has the potential to disrupt the cytotoxic cascade and preserve epithelial integrity in patients with CeD. However, the use of monoclonal antibodies in CeD raises several important concerns. Their production is expensive, and widespread clinical use would likely impose a significant financial burden on both patients and healthcare systems. Moreover, the long-term safety of monoclonal antibodies remains uncertain. Therefore, future, long-term clinical trials are needed to asses not only their therapeutic efficacy but also safety and cost-effectiveness.

9. Conclusions

To date, strict, lifelong adherence to a GFD remains the only officially recommended treatment for CeD. While effective in acquiring mucosal healing and symptom resolution in many patients, the diet requires rigorous adherence, which can be challenging to maintain due to the widespread presence of gluten and the high risk of inadvertent exposure. Importantly, a significant proportion of patients—despite reporting adherence to a GFD— fail to achieve complete clinical or histological remission. These individuals may benefit from pharmacological interventions that either complement or replace the GFD by suppressing the immune response triggered by gluten ingestion. Although several promising therapeutic targets have been identified, including TG2, IL-15, HLA-DQ2, and gluten complexes, as well as lymphocyte trafficking pathways, many investigational treatments remain in early-phase development or have been discontinued without publishing their results. Among the most promising strategies are TG2 inhibitors and monoclonal antibodies targeting IL-15. However, their long-term efficacy and safety are yet to be investigated. Therefore, future research should prioritize large-scale, randomized clinical trials with standardized endpoints and explore personalized approaches to improve long-term outcomes and quality of life for patients with CeD.

Author's contribution:

Conceptualization, A.K. and A.S.; Methodology, A.K., A.R., and A.G.; Software, N.G. and M.W.; Validation: P.L. and M.W.; Formal analysis: A.K. and A.G.; Investigation: P.L. and N.G.; Resources: A.S. and A.R.; Data curation: P.L. and A.K.; Writing- Original- draft preparation: A.K., A.S. and A.R.; Writing- review and editing: M.W. and N.G.; Supervision: A.R. and P.L.; Project administration: A.K., A.G., M.W., N.G., A.S., P.L., A.R.

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