Fighting Celiac Disease from Different Aspects: New Approaches to Treatment beyond the Gluten-free Diet

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INTRODUCTION

Celiac disease (CeD) is an immune-mediated enteropathy occurring in genetically predisposed individuals carrying variants of the human leukocyte antigen (HLA) DQ2 and DQ8 genes. Its global prevalence rate is approximately 1.4% [1]. It is characterized by intestinal wall inflammation and malabsorption resulting from dietary intake of gluten proteins found in wheat, rye, and barley. These peptides cross into the submucosa, where they undergo deamination by tissue transglutaminase and bind to HLA-DQ2 or HLA-DQ8 on antigen-presenting cells, triggering T-cell activation. This immune response leads to infiltration of the epithelium and lamina propria by chronic inflammation cells and destruction of the intestinal villi [2].

Clinically, CeD is classified as classic, atypical, subclinical, potential, latent or refractory. It typically presents with malabsorption and symptoms such as abdominal pain, flatulence, steatorrhea, and weight loss. However, up to 50% of patients exhibit an atypical clinical presentation, with extraintestinal manifestations such as anemia, osteopenia, osteoporosis, arthralgia, menstrual cycle disorders, infertility, neuropsychiatric disorders, enamel tooth hypoplasia, alopecia, herpetic dermatitis, childhood growth retardation, etc.

Diagnosis requires a combination of serological, histological, and clinical findings, while treatment involves lifelong exclusion from gluten from the diet and a nutritious diet to meet the needs of the body [3].

The lack of effective pharmacological treatments for CeD is primarily attributed to the complexity of its pathogenesis, and the challenge of identifying an optimal target to address the multifaceted needs of patients. In this editorial, we primarily review current experimental therapies targeting various pathological aspects of the disease.

Therapy strategies beyond gluten-free diet

The various tested therapies that have emerged at the scientific forefront in recent years, intending to improve the quality of life of patients with gluten intolerance, could be categorized according to their therapeutic strategy and the specific point of the pathophysiological pathway they target.

A. Reducing Gluten Immunogenicity

Reduction of gluten immunogenicity has been achieved through genetic modification of gluten-containing foods. An example is the E82 wheat line, which is produced by RNAi technology that blocks relevant gliadin genes [4]. Pretreatment of flours or sourdoughs with microbial transglutaminase and N-methyl-lysine, or with probiotic bacteria of the genus Lactobacillus

Abbreviations: *CeD, Celiac disease; HLA, Human leukocyte antigen; tTG, tissue Transglutaminase; TG2, Transglutaminase II; IL-2, Interleukin 2; IFN-γ, Interferon γ; IL-17, Interleukin 17; IL-15, Interleukin15; mAb, monoclonal Antibody; IL-23, Interleukin 23.*

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(VSL#3), produces tolerable predigested gliadins without immunogenic peptides [5,6].

Transglutaminase II (TG2) inhibitors prevent the degradation of gluten peptides to form immunogenic complexes by inhibiting tissue transglutaminase activity. As a result, gluten-induced T-cell activation in the intestinal mucosa is reduced. Furthermore, TG2 inhibition has been shown in vitro to regulate intestinal epithelial permeability functions [7]. In a proof-of-concept trial, patients who received a six-week treatment with ZED1227, a selective oral TG2 inhibitor at a dosage of 100 mg, demonstrated significant improvement in symptoms and quality-of-life scores when compared to placebo [8].

AGY-010, an egg yolk anti-gliadin polyclonal antibody, and BL-7010 Copolymer P (HEMA-co-SS), which interacts with α-gliadin, are molecules that achieve gluten binding in the intestinal lumen. Specifically, AGY-010 neutralizes gluten proteins, preventing their degradation into immunogenic peptides. Results regarding the safety and efficacy of AGY capsules from a Phase 2 randomized, double-blind, placebo-controlled, crossover trial, are pending (NCT03707730) [9].

Gluten digestion through exogenous peptidases such as AN-PEP, Latiglutenase and Zamaglutenase, is another neutralization strategy. Latiglutenase (formerly known as ALV003) combines two gluten-specific recombinant proteases and is the most investigated molecule in human trials. In summary, the results of the studies suggest that ALV003 has the potential to mitigate the symptoms and histological damage caused by gluten, particularly in patients with positive serological markers [10]. Zamaglutenase (formerly known as TAK-062) is a computer-designed endopeptidase that targets the proline-glutamine dipeptide and has been shown to degrade over 99% of gluten in complex meals in both in vitro and Phase 1 in vivo studies [11]. AN-PEP is an Aspergillus Niger prolyl endoprotease that degrades into non-immunogenic residues, gluten and gluten peptides ingested with food [12]. Currently, several over-the-counter digestive enzyme supplements such as GliadinX, GluteZym and GluteoStop, are available, the effectiveness of which is controversial [12]. The results from the clinical studies on the efficacy of AN-PEP compared to placebo showed no significant differences in terms of worsening of CeD-related quality scores or antibody titers [13].

TIMP-GLIA (formerly TAK-101) is a nanoparticle for gliadin presentation. It induced sustained unresponsiveness to gluten in mice and showed inhibition of cytokines IL-2, IFN-γ, and IL-17, as well as reduced secretion of gliadin-stimulated T cells. In a Phase II trial, a 14-day gluten challenge in 33 patients showed an 88% reduction in IFN-γ spot-forming units compared to placebo.

B. Modification of the immune response

Inhibition of T-cell activation through HLA-DQ blockage is another therapeutic strategy. A multispecific antibody, DONQ52, was recently tested in HLA-DQ2.5+ patients (N=44) after a three-day grain challenge. DONQ52 inhibited the wheat gluten-specific T-cell response and reduced barley hordein and rye secalin T-cell responses [14].

Modifying the migration of gut-tropic lymphocytes to the intestinal mucosa is an alternative approach. Vercirnon (a CCR9 antagonist) and α4β7 integrin antagonists, such as Vedolizumab and PTG-100, could be useful for treating subsets of CeD patients. Results from Phase Ib and Phase II trials for PTG-100 and Vercirnon, respectively, are awaited [15].

Interleukin-15 (IL-15) is a critical component in the activation of intraepithelial lymphocytes and natural killer cells in CeD patients. PRN-015 (formerly AMG714), a humanized IgG1 anti-IL15 monoclonal antibody (mAb) and Hu-Mik-β1, an anti-IL15Rβ1 mAb, are currently undergoing Phase I testing in patients with refractory CeD [16]. Tofacitinib, a pan-JAK inhibitor, has demonstrated the potential to reverse the pathological manifestations of IL-15 overexpression, as evidenced in a transgenic celiac mouse model study [15].

Other immunomodulatory agents that have been used off label in isolated refractory cases are infliximab, an anti-TNFα agent, and rituximab, an anti-CD20 mAb. In some cases, symptomatic improvement has been observed, but larger randomized trials are lacking [17]. Budesonide, an oral glucocorticoid, has been studied in patients with both refractory and non-refractory CeD, possibly conferring clinical benefit while achieving better tolerance compared to systemic corticosteroids [14].

C. Induction of immunetolerance

Nexvax2 is a desensitizing vaccine with three gluten peptides, based on the immunotolerant training of CD4+ T lymphocytes through targeted gluten epitopes. Although in a Phase I clinical trial, Nexvax2 was well tolerated in HLA-DQ2+ patients, Phase II trial (RESET CeD) was discontinued due to lack of efficacy [18].

KAN-101 is based on the coupling of gluten immunogenic peptides to erythrocytes. It harnesses natural

tolerance through hepatic degradation, by activating Tregs, reducing the inflammatory response following gluten challenge. It is currently being evaluated in Phase Ib/II and Phase II trials [16].

Controlled parasitic infection with Necator americanus aims to suppress gluten-induced expansion of IFN-γ, IL-17, and IL-23, through intestinal immune homeostasis. Although results from a Phase I/II study showed no significant histological changes, further investigation in celiac patients experiencing occasional gluten exposure is needed [14].

D. Modulation of the interaction between gluten and epithelium

An alternative approach entails the reinforcement of the intestinal barrier, intending to prevent gluten translocation and the subsequent immune activation. One of the most studied agents is larazotide acetate (AT1001), a zonulin inhibitor that modulates tight junction integrity, reducing paracellular gut permeability. Despite the demonstrable efficacy and safety of larazotide in treating patients with persistent disease in a Phase IIb trial, Phase III trial was halted due to limited patient sample [19].

IMU-856 is an orally available small molecule that epigenetically regulates epithelial regeneration. Acting via upregulation of SIRT6, a sirtuin family protein involved in chromatin remodeling and transcriptional control of genes, maintains intestinal barrier function and promotes epithelial restoration of villous architecture [19]. In a Phase Ib trial that incorporated a 15-day gluten challenge, IMU-856 exhibited favorable outcomes in comparison with placebo. A reduction in gluten-induced mucosal damage was found based on measurements of the height of villi. Furthermore, IMU-856 improved or reversed disease-related symptoms, including bloating and fatigue [20].

CONCLUSIONS

In conclusion, the emergence of a variety of therapeutic strategies beyond the gluten-free diet represents a significant development in the management of CeD. These investigational agents target various aspects of CeD pathophysiology, ranging from enzymatic gluten degradation to immune modulation and intestinal barrier repair. The complexity and variability of CeD indicates the potential need for a personalized therapeutic approach, and the development of new treatments may contribute to this goal.

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