Refractory Celiac Disease: from basic insights to therapy

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Celiac disease: new therapies on the horizon

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Abstract

Celiac Disease (CeD) is a chronic intestinal disease which occurs in 0.7-1.4% of the global population. Since the discovery of gluten as its disease-inducing antigen, CeD patients are treated with a gluten-free diet which is effective but has limitations for certain groups of patients. Accordingly, over the past few years, there is a growing interest in alternative treatment options. This review summarizes emerging pharmacological approaches, including tolerance induction strategies, tissue transglutaminase inhibition, gluten degradation, and inhibition of interleukin (IL)-15.

Introduction

CeD is a chronic inflammatory disorder of the gut mediated by the ingestion of gluten in genetically susceptible individuals. Upon gluten ingestion, gluten peptides cross the epithelial barrier and are deamidated by the enzyme tissue transglutaminase 2 (TG2). These negatively charged gluten peptides bind efficiently to HLA-DQ2/8 molecules on antigen-presenting cells (APCs), triggering gluten-specific CD4 T cells and small-intestinal mucosal injury mediated by interferon-ɣ (IFN-ɣ), tumor necrosis factor α (TNF-α), IL-2, IL-21 and IL-15. Gluten-specific memory CD4 T cells are continuously on guard, respond to gluten intake within 6 hours with release of inflammatory mediators such as IL-2[1] and accompanying symptoms such as nausea and vomiting.[2] One of the main unresolved questions in CeD relates to the question what triggers the loss of tolerance to gluten peptides, although a role for the microbiota and/or viral/bacterial infections has been implied.

Since the discovery of gluten peptides as the disease-inducing antigen, a life-long gluten-free diet (GFD) is the only treatment option for CeD. Strict adherence to a GFD has substantial financial and social implications. Moreover, full mucosal healing is not reached in approximately 40% of CeD patients.[3] For these reasons, there is a growing interest in non-dietary treatment options. CeD is an attractive disease for therapeutic development since many key mechanisms of disease pathogenesis have been unraveled. Novel therapies can theoretically interfere with these mechanisms at several stages of disease pathogenesis. Broadly, this can be at the level of disease prevention or at the level of treatment of disease. Since the trigger for a loss of tolerance to gluten peptides needs further elucidation, we need to focus on strategies targeting the inflammatory cascade. **(Figure 1)**

This short review summarizes and discusses drug targeted therapies that are currently in advanced phases of clinical evaluation, including failed studies from which lessons can be drawn. We summarize strategies that are currently in preclinical stages of development and in phase 1 clinical trials in Table 1. Lastly, we will give our view on future perspectives of targeted therapeutics in CeD.

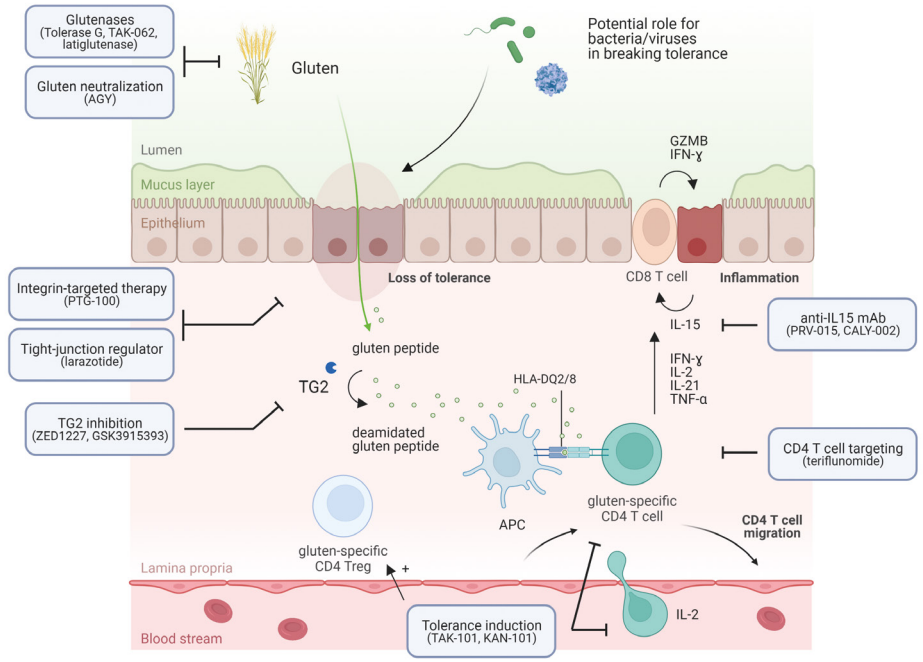

Figure 1. Potential therapies currently under investigation in vivo.

In celiac disease (CeD), gluten peptides cross the epithelial barrier, are deamidated by the enzyme tissue transglutaminase 2 (TG2) and loaded onto HLA-DQ2/8 molecules on antigen-presenting cells (APCs) which leads to activation of gluten-specific CD4 T cells. Upon activation, these gluten-specific CD4 T cells secrete cytokines such as interferon-ɣ (IFN-ɣ), interleukin (IL)-2, IL-21 and tumor necrosis factor α (TNF-α). These cytokines mediate small-intestinal mucosal injury in cooperation with IL-15, produced by epithelial cells upon inflammation. Intra-epithelial cytotoxic CD8 T cells are activated and secrete cytokines such as granzyme B (GZMB) and IFN-ɣ, creating a vicious cycle of small-intestinal inflammation. In the periphery, gluten-specific memory CD4 T cells are continuously on guard and respond within 6 hours to gluten intake with release of inflammatory mediators such as IL-2. There is a potential role for bacterial/viral infections in in breaking oral tolerance to gluten proteins. Treatment strategies currently under investigation in vivo target different aspects of CeD pathogenesis. Glutenases and the anti-gliadin antibody AGY target gluten proteins; integrin-targeted therapies and tight-junction regulators aim at improvement of barrier function; TG2 inhibitors aim at preventing the deamidation of gluten peptides; anti-IL15 monoclonal antibodies (mAbs) target the inflammatory cytokine IL-15; CD4 T cell targeting strategies target inhibition of rapidly expanding gluten-specific CD4 T cells; tolerance induction strategies aim at clonal anergy/deletion of gluten-specific CD4 T cells and promotion of gluten-specific CD4 regulatory T cell (Treg) differentiation. Abbreviations: APC, antigen-presenting cell; CeD, celiac disease; GZMB, granzyme B; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; mAbs, monoclonal antibodies; TG2, tissue transglutaminase 2; TNF, tumor necrosis factor; Treg, T regulatory cell.

Table 1. CeD Clinical Pipeline: Targeted Drug Therapies .

Pre-Clinical		
Drug	**Therapeutic approach**	**Reference**
ALL-001	Oral tolerogenic immunotherapy	Sanchez-Solares et al., 2021[4]
AG017	Oral tolerogenic immunotherapy	-
BNZ-2	Cytokine targeting of IL-15/IL-21	Ciszewski et al., 2020[5]
E40	Glutenase	Cavaletti et al., 2019[6]

Phase 1			
Drug	**Therapeutic approach**	**Status**	**Identifier**
KAN-101	Tolerogenic immunotherapy	completed, results awaited	ClinicalTrials.gov, NCT04248855
PTG-100	Integrin-targeted therapy	ongoing	ClinicalTrials.gov, NCT04524221
GSK3915393	TG2-inhibitor	ongoing	ClinicalTrials.gov, NCT04604795
CALY-002	anti-IL-15 mAb	ongoing	ClinicalTrials.gov, NCT04593251

Tolerance induction strategies

Loss of tolerance towards gluten peptides triggers CeD pathogenesis. Therefore, the ideal treatment strategy would be an in vivo tolerance-inducing agent, which would reinstate tolerance to gluten and thus allows patients to consume dietary gluten. Such an approach might utilize tolerogenic dendritic cells (tolDCs) which promote an anti-inflammatory environment, induce clonal anergy or deletion of antigen-specific T cells and promote antigen-specific regulatory T cell (Treg) differentiation, thus suppressing gluten-specific CD4 T cells in CeD. **(Figure 1)**

The Nexvax2 study attempted to induce tolerance through dermal vaccination of three saline-dissolved immunodominant gluten peptides. CeD patients on a GFD received multiple doses of NexVax2 or placebo followed by a double-blind placebo-controlled oral gluten challenge. Although first results showed signs indicative for peripheral tolerance, during interim analysis, it was shown that NexVax2 failed to prevent development of villous atrophy and CeD-associated symptoms upon gluten challenge.[7-9]

An incorrect route of administration is the most plausible reason for failure of Nexvax2. Likely, in the absence of tolerizing agents, gluten peptides induced inflammatory rather than tolerizing responses. In agreement, all three peptides were detected in plasma samples of the patients 45 minutes post-injection. It is therefore likely that these free peptides triggered peripheral and/or intestinal gluten-specific CD4 T cells, leading to villous atrophy and CeD-associated symptoms.

Another approach uses intravenous administration of nanoparticles used for encapsulation of gluten protein extract (TAK-101), ensuring the presence of a broad range of gluten epitopes.[10] These nanoparticles reach secondary lymphoid organs, such as spleen and liver, where they are processed by macrophages and/or DCs. In a mouse model for CeD, administration of nanoparticles increased mRNA levels of FoxP3 in splenocytes and inhibited IFN-ɣ secretion by and proliferation of gluten-reactive T cells, consistent with tolerance induction.[11] Importantly, this concept was tested in a recent randomized clinical study.[10] Patients were infused at day 1 and day 8 with nanoparticles, followed by a 14-day gluten challenge, starting 7 days post-infusion. After a 6-day gluten challenge, the placebo group showed an increase in circulating gluten-reactive (IFN-ɣ$^+$) CD4 T cells, Treg cells and activated CD8 and γδ T cells, whereas these cells were decreased in the nanoparticle treated group. Despite this decrease in gluten-induced peripheral reactivity, only a minor improvement in duodenal mucosal injury was observed. Moreover, in both groups, an increase in intra-epithelial lymphocytes (IELs) of unknown phenotype was observed. Additionally, injection of nanoparticles did not lead to an increase in peripheral Tregs. However, it may be that antigen-specific Treg cells localize at the site of antigen presentation. Overall, the TAK-101 nanoparticle approach may have merits but a more definitive evaluation awaits substantially larger clinical studies.

In vivo tolerance induction is an attractive treatment strategy for CeD as the disease-inducing T-cell epitopes are known.[12] However, multiple questions need to be addressed. For CeD specifically, studies have shown an impaired function of peripheral FoxP3$^+$ Tregs.[13,14]

It is of interest to assess if induced FoxP3$^+$ Tregs are antigen-specific, secrete IL-10 and if induced tolDCs are capable of reprogramming FoxP3$^+$ Tregs in CeD. More generic questions regarding tolerogenic immunotherapy are about method of administration and optimal dosing/timing strategies. Also, there is uncertainty about the duration of the tolerogenic response and whether it is maintained after inflammatory signals which disrupt the balance, such as a gastrointestinal infections. Although further investigation is needed, the first steps have been made towards tolerance induction in CeD.

Gluten degradation by glutenases

Oral enzyme therapy for CeD is attractive, since immunogenic gluten peptides are initiators of the pathogenic cascade. First peptidase therapies used proteases, shown to be highly efficient in decreasing immunogenicity of proline-rich gluten peptides in vitro[15, 16]. However, this was not consistently reflected in various in vivo studies[17-22]. This is attributed to an impact of the acidic environment in the stomach on the degradation efficiency and interference of other dietary components.[23] Nevertheless, the acid-resistant enzyme Aspergillus Niger-derived prolyl endopeptidase (AN-PEP) is now currently commercially available (Tolerase G). Moreover, randomized phase 2 trials are ongoing with latiglutenase (IMGX003, formerly ALV003) (ClinicalTrials.gov, NCT03585478) although previous studies have shown conflicting results regarding its effect on villous atrophy and clinical symptoms, and a gluten degradation efficiency of only 88%.[18, 19]

A phase 1 study evaluating a newly engineered endopeptidase (TAK-062)[24], targeting proline and glutamine peptide motifs simultaneously was recently published.[25] In this study, healthy individuals ingested TAK-062 before a complex meal containing 1-6 gram gluten. Efficiency of gluten degradation at 20-65 min post-TAK-062, showed 97-99% gluten degradation in aspirate samples from the stomach. However, calculated residual gluten showed median amounts up to 38 mg. This is potentially of clinical relevance, since amounts as low as 10 mg gluten may be able to trigger the immunological cascade.[26, 27] Yet, these data show high potency of TAK-062, and further studies in CeD patients are awaited.

Tissue transglutaminase inhibition

Inhibition of intestinal TG2 prohibits deamidation of gluten peptides and prevents an unsolicited gluten-specific CD4 T cell response. (Figure 1) In 2018, proof-of-concept for this strategy was shown in a mouse model of intestinal inflammation.[28] This was followed by a phase 2, randomized, placebo-controlled trial in patients with CeD.[29] Daily oral administration of ZED1227 for 6 weeks combined with a daily 3 gram gluten-challenge decreased mucosal injury in CeD patients, as measured by villous height to crypt depth ratio. Most common adverse events (AEs), of similar incidence in placebo and treatment groups, were of gastrointestinal nature, including nausea, vomiting, diarrhea and abdominal pain. Possibly, this is attributed to the fact that ZED1227 was administered only 30 minutes before the gluten challenge. However, since the nature of these AEs could also indicate gluten-reactivity, it is crucial to perform additional studies. Nonetheless, this is the first pharmacological approach that has shown signs of protection towards gluten-induced mucosal injury.

Cytokine targeting by monoclonals

IL-15 is an important inflammatory driver in CeD, produced by intestinal epithelial cells and lamina propria cells.[30] Overexpression of IL-15 stimulates intra-epithelial cytotoxic CD8 T cells, leading to intestinal tissue destruction. **(Figure 1)**

The first trial targeting IL-15 evaluated an anti-IL-15 monoclonal antibody (mAb) (AMG 714).[31] In this randomized, placebo-controlled trial, CeD patients on a GFD were challenged with 2-4 gram daily gluten and were injected every two weeks with a total of six doses anti-IL-15 mAb. Results showed signs of improvement in clinical symptoms, particularly diarrhea. However, results did not show prevention of villous atrophy and an increase in IEL density was reported. Despite these results, further assessment of AMG 714 is continued (under the name PRV-015) in a randomized phase 2 trial with CeD patients (ClinicalTrials.gov, NCT04424927). Irrespective of its potential as a therapeutic it should be noted that monoclonals are expensive and require maintenance therapy.

Improving barrier function

In CeD, paracellular permeability is increased by intestinal inflammation. Larazotide acetate is a single-chain eight-amino acid peptide that is believed to act as a tight junction regulator, capable of restoring intestinal barrier function. A randomized study in 342 CeD patients treated with different doses of larazotide showed mixed results, with only the lowest dose of 0.5 mg showing an effect on clinical symptoms.[32] Higher doses did not differ from placebo and no effects on intestinal mucosa were reported. The role of larazotide in the treatment of CeD is under debate as there is no rationale for the proposed mode of action.[33, 34] Nevertheless, this compound is currently investigated in a phase 3 clinical trial (ClinicalTrials.gov, NCT03569007).

Conclusion

A GFD is a safe and effective treatment for the majority of CeD patients. Any new treatment has to be at least as effective and safe in order to justify the higher costs that are inevitably associated with a pharmacological treatment. Having said that, there is an unmet need for certain groups of patients who may benefit from novel treatment modalities currently under investigation.

With several novel treatment options on the horizon, the treatment of CeD has entered an exciting new era. Preventing the onset of CeD entirely would be the most desirable approach but studies with early or delayed introduction of gluten have not proven to be effective. Other preventative measures such as vaccines for enteroviruses[35, 36], reoviruses[37] and bacteria, may prove effective but this awaits evaluation.

Novel therapeutics preferably aim at immunological components either upstream or at the level of gluten-reactive CD4 T cells rather than targeting downstream inflammatory events.

Targeting gluten, TG2, APCs for tolerization, and gluten-reactive CD4 T cells themselves all fulfil this requirement. In this respect, the results of the phase 2 trial with teriflunomide (ClinicalTrials.gov, NCT04806737), which targets rapidly proliferating lymphocytes i.e. gluten-reactive CD4 T cells will be of interest.

Among the drugs that are currently under clinical investigation, tolerance induction with nanoparticles loaded with gluten extract (TAK-101) and inhibition of TG2 are of interest since they are so far the only ones to show a decrease of gluten-induced mucosal injury.

Other drugs, including PRV-015 (AMG 714) and the anti-gliadin antibody (AGY)[38] (currently in a phase 2 clinical trial (ClinicalTrials.gov, NCT03707730)), have shown signs of efficacy in terms of improvement in clinical symptoms, but their effect on mucosal injury needs to be established. With regard to enzyme therapy, TAK-062 is the first to show a highly efficient gluten-degradation capacity in vivo, an essential prerequisite for prevention of a gluten-specific CD4 T cells response in the small intestine. In this regard, it should be noted that CeD patients show varying immunological and clinical responses to different amounts of gluten.[39] Whether such enzymes are capable to effectively and reliably neutralize an entire gluten containing meal awaits further investigation. Alternatively, such enzymes can be used as an adjunct to a GFD to prevent symptoms due to gluten contamination.

In conclusion, research in the field of novel treatment modalities for CeD is very active and treatments under investigation hold promise for the unmet needs of CeD patients. Before they can be incorporated in the treatment armamentarium, several key question relating to efficacy and safety endpoints have to be answered. Until then, the GFD remains the gold standard for the treatment of CeD.

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Author contributions
TD, FK and GB jointly wrote the manuscript. TD designed the figures.

Competing interests
None to declare.

References

1. Goel G, Tye-Din JA, Qiao S-W, et al. Cytokine release and gastrointestinal symptoms after gluten challenge in celiac disease. Science Advances 2019;5:eaaw7756.

2. Tye-Din JA, Daveson AJM, Goldstein KE, et al. Patient factors influencing acute gluten reactions and cytokine release in treated coeliac disease. BMC Medicine 2020;18:362.

3. Rubio-Tapia A, Rahim MW, See JA, et al. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. The American journal of gastroenterology 2010;105:1412-1420.

4. Sanchez-Solares J, Sanchez L, Pablo-Torres C, et al. Celiac Disease Causes Epithelial Disruption and Regulatory T Cell Recruitment in the Oral Mucosa. 2021;12.

5. Ciszewski C, Discepolo V, Pacis A, et al. Identification of a γc Receptor Antagonist That Prevents Reprogramming of Human Tissue-resident Cytotoxic T Cells by IL15 and IL21. Gastroenterology 2020;158:625-637.e13.

6. Cavaletti L, Taravella A, Carrano L, et al. E40, a novel microbial protease efficiently detoxifying gluten proteins, for the dietary management of gluten intolerance. Scientific Reports 2019;9:13147.

7. Truitt KE, Daveson AJM, Ee HC, et al. Randomised clinical trial: a placebo-controlled study of subcutaneous or intradermal NEXVAX2, an investigational immunomodulatory peptide therapy for coeliac disease. Alimentary Pharmacology and Therapeutics 2019;50:547-555.

8. Daveson AJM, Ee HC, Andrews JM, et al. Epitope-Specific Immunotherapy Targeting CD4-Positive T Cells in Celiac Disease: Safety, Pharmacokinetics, and Effects on Intestinal Histology and Plasma Cytokines with Escalating Dose Regimens of Nexvax2 in a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study. EBioMedicine 2017;26:78-90.

9. Goel G, King T, Daveson AJ, et al. Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: two randomised, double-blind, placebo-controlled phase 1 studies. The Lancet Gastroenterology & Hepatology 2017;2:479-493.

10. Kelly CP, Murray JA, Leffler DA, et al. TAK-101 Nanoparticles Induce Gluten-Specific Tolerance in Celiac Disease: A Randomized, Double-Blind, Placebo-Controlled Study. Gastroenterology 2021.

11. Freitag TL, Podojil JR, Pearson RM, et al. Gliadin Nanoparticles Induce Immune Tolerance to Gliadin in Mouse Models of Celiac Disease. Gastroenterology 2020;158:1667-1681.e12.

12. Sollid LM, Tye-Din JA, Qiao S-W, et al. Update 2020: nomenclature and listing of celiac disease–relevant gluten epitopes recognized by CD4+ T cells. Immunogenetics 2020;72:85-88.

13. Granzotto M, dal Bo S, Quaglia S, et al. Regulatory T-Cell Function Is Impaired in Celiac Disease. Digestive Diseases and Sciences 2009;54:1513-1519.

14. Cook L, Munier CML, Seddiki N, et al. Circulating gluten-specific FOXP3+CD39+ regulatory T cells have impaired suppressive function in patients with celiac disease. Journal of Allergy and Clinical Immunology 2017;140:1592-1603.e8.

15. Marti T, Molberg Ø, Li Q, et al. Prolyl endopeptidase-mediated destruction of T cell epitopes in whole gluten: Chemical and immunological characterization. Journal of Pharmacology and Experimental Therapeutics 2005;312:19-26.

16. Stepniak D, Spaenij-Dekking L, Mitea C, et al. Highly efficient gluten degradation with a newly identified prolyl endoprotease: implications for celiac disease. American Journal of Physiology-Gastrointestinal and Liver Physiology 2006;291:G621-G629.

17. Pyle GG, Paaso B, Anderson BE, et al. Effect of pretreatment of food gluten with prolyl endopeptidase on gluten-induced malabsorption in celiac sprue. Clinical Gastroenterology and Hepatology 2005;3:687-694.

18. Lähdeaho M-L, Kaukinen K, Laurila K, et al. Glutenase ALV003 Attenuates Gluten-Induced Mucosal Injury in Patients With Celiac Disease. Gastroenterology 2014;146:1649-1658.

19. Murray JA, Kelly CP, Green PHR, et al. No Difference Between Latiglutenase and Placebo in Reducing Villous Atrophy or Improving Symptoms in Patients With Symptomatic Celiac Disease. Gastroenterology 2017;152:787-798.e2.

20. Tack GJ, van de Water JMW, Bruins MJ, et al. Consumption of gluten with gluten-degrading enzyme by celiac patients: a pilot-study. World journal of gastroenterology 2013;19:5837-5847.

21. Salden BN, Monserrat V, Troost FJ, et al. Randomised clinical study: Aspergillus niger-derived enzyme digests gluten in the stomach of healthy volunteers. Alimentary pharmacology & therapeutics 2015;42:273-285.

22. König J, Holster S, Bruins MJ, et al. Randomized clinical trial: Effective gluten degradation by Aspergillus niger-derived enzyme in a complex meal setting. Scientific Reports 2017;7:13100.

23. Montserrat V, Bruins MJ, Edens L, et al. Influence of dietary components on Aspergillus niger prolyl endoprotease mediated gluten degradation. Food Chemistry 2015;174:440-445.

24. Wolf C, Siegel JB, Tinberg C, et al. Engineering of Kuma030: A Gliadin Peptidase That Rapidly Degrades Immunogenic Gliadin Peptides in Gastric Conditions. Journal of the American Chemical Society 2015;137:13106-13113.

25. Pultz IS, Hill M, Vitanza JM, et al. Gluten Degradation, Pharmacokinetics, Safety, and Tolerability of TAK-062, an Engineered Enzyme to Treat Celiac Disease. Gastroenterology 2021;161:81-93.e3.

26. Catassi C, Fabiani E, Iacono G, et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. The American Journal of Clinical Nutrition 2007;85:160-166.

27. Leonard MM, Silvester JA, Leffler D, et al. Evaluating Responses to Gluten Challenge: A Randomized, Double-Blind, 2-Dose Gluten Challenge Trial. Gastroenterology 2021;160:720-733.e8.

28. Ventura MAE, Sajko K, Hils M, et al. Su1161 - The Oral Transglutaminase 2 (TG2) Inhibitor Zed1227 Blocks TG2 Activity in a Mouse Model of Intestinal Inflammation. Gastroenterology 2018;154:S-490.

29. Schuppan D, Mäki M, Lundin KEA, et al. A Randomized Trial of a Transglutaminase 2 Inhibitor for Celiac Disease. New England Journal of Medicine 2021;385:35-45.

30. Di Sabatino A, Ciccocioppo R, Cupelli F, et al. Epithelium derived interleukin 15 regulates intraepithelial lymphocyte Th1 cytokine production, cytotoxicity, and survival in coeliac disease. Gut 2006;55:469-477.

31. Lähdeaho M-L, Scheinin M, Vuotikka P, et al. Safety and efficacy of AMG 714 in adults with coeliac disease exposed to gluten challenge: a phase 2a, randomised, double-blind, placebo-controlled study. The Lancet Gastroenterology & Hepatology 2019;4:948-959.

32. Leffler DA, Kelly CP, Green PHR, et al. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: a randomized controlled trial. Gastroenterology 2015;148:1311-9.e6.

33. Sollid LM, Koning F. Lack of relationship of AT1001 to zonulin and prehaptoglobin-2: clinical implications. Gut 2021;70:2211.

34. Massier L, Chakaroun R, Kovacs P, et al. Blurring the picture in leaky gut research: how shortcomings of zonulin as a biomarker mislead the field of intestinal permeability. Gut 2021;70:1801.

35. Kahrs CR, Chuda K, Tapia G, et al. Enterovirus as trigger of coeliac disease: nested case-control study within prospective birth cohort. BMJ 2019;364:l231.

36. Oikarinen M, Puustinen L, Lehtonen J, et al. Enterovirus Infections Are Associated With the Development of Celiac Disease in a Birth Cohort Study. Frontiers in immunology 2021;11:604529-604529.

37. Bouziat R, Hinterleitner R, Brown JJ, et al. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. Science 2017;356:44.

38. Sample DA, Sunwoo HH, Huynh HQ, et al. AGY, a Novel Egg Yolk-Derived Anti-gliadin Antibody, Is Safe for Patients with Celiac Disease. Digestive Diseases and Sciences 2017;62:1277-1285.

39. Montgomery AM, Goka AK, Kumar PJ, et al. Low gluten diet in the treatment of adult coeliac disease: effect on jejunal morphology and serum anti-gluten antibodies. Gut 1988;29:1564.