Anti-IL-15 monoclonal antibody for the treatment of coeliac disease: the light at the end of the gluten free diet tunnel?

Stefan L. Popa[1], Giuseppe Chiarioni[2,3]

[1]2nd Medical Department, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2]Division of Gastroenterology of the University of Verona, AOUI Verona, Italy; [3]Division of Gastroenterology and Hepatology & Center for Functional GI and Motility Disorders, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Correspondence to: Giuseppe Chiarioni, MD, RFF. Division of Gastroenterology of the University of Verona, AOUI Verona, Italy; Division of Gastroenterology and Hepatology & Center for Functional GI and Motility Disorders, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. Email: chiarioni@alice.it.

Comment on: Lähdeaho ML, Scheinin M, Vuotikka P. 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;4:948-59.

Coeliac disease (CD) background

CD is a chronic immune-mediated enteropathy triggered by gluten ingestion in genetically predisposed subjects (1). In CD the immunology response to gluten causes histology abnormalities of the small bowel mucosa eventually leading to villous atrophy and secondary vitamins, and nutrients malabsorption (1,2). In affected individuals, recent evidence suggests that gluten evokes a signaling cascade which triggers an inflammatory reaction with cytokine release resulting in additional intestinal mucosal barrier dysfunction for damage of tight junction proteins (e.g., Zonulin), so called "leaky gut" syndrome (2). The increased intestinal permeability allows gluten peptides to reach the lamina propria via either a para-cellular or intracellular route thus aggravating inflammation with systemic complications (2,3). A recent meta-analysis provided evidence of increasing incidence of celiac disease in the western world mostly in the pediatric population and in females (4). In the 21st century, the pooled female incidence of CD was 17.4 new cases per 100,000 person-years, compared with 7.8 in males. When considering the pediatric incidence, it was found to be 21.3 per 100,000 person-years compared to 12.9 in adults (4). Notwithstanding this data, CD recognition can be challenging with functional gastrointestinal disorders frequently misdiagnosed instead (1,5). Moreover, CD shows a complex clinical scenario from life-threatening manifestations of severe malabsorption to minimally symptomatic or even non-symptomatic presentations. The clinical picture of adult CD is dominated by gastrointestinal symptoms: diarrhea, bloating, flatulence, abdominal pain, while systemic manifestations (e.g., weight loss, fatigue) are less common. However, extra intestinal manifestations might include: dermatological symptoms (dermatitis herpetiformis), neurologic symptoms (seizures, motor weakness, paresthesia and ataxia) and hormonal imbalance of both reproductive and infertility ages (1). Current guidelines recommend plasma testing of anti-transglutaminase antibody to screen for CD in both adults and children when symptoms are suggestive and/or at high genetic risk as first degree relative of CD patients (1). However, duodenal biopsies are still mandatory to confirm the diagnosis in adults (1). Main histopathologic characteristics of CD include modifications of the small intestine mucosa: deteriorated villi with a decreased villous-to-crypt ratio (VHCD), hyperplastic crypts, with increased number of intraepithelial lymphocytes (IEL) per unit length of absorptive epithelium (normal IEL to epithelial cell ratio, 1:10) (2). Architectural changes in the mucosa can be precisely quantified and analyzed using the VHCD. The normal VHCD is considered between 4–5:1. A lower VHCD ratio indicates a levelling of the small bowel absorptive surface , severe intestinal injury, and progressive clinical deterioration (2).

Gluten free diet (GFD) and alternative treatment approach

Mainstay treatment in CD is lifelong avoidance of gluten containing foods to reverse the inflammatory bowel response and normalize histology (1). Moreover, GFD should be strict with focused attention to gluten cross-contaminations (1,2). However, avoiding contamination can be challenging for plenty of products contain hidden gluten and even gluten-free-labeled products might contains traces of gluten (6). This is of major concern for up 20% of CD patients following a GFD might report bowel and abdominal symptoms (1,7). In addition, compliance to a long lasting GFD is challenging for most patients and a diverse treatment approach is a demanding issue. To decrease the toxic effect of gluten in CD different strategies have been explored by means of various molecular biology, microbial, enzymatic, and pharmaceutical approaches (7).

Common strategy used to reduce CD pathogenicity includes specific probiotic strains which grow in the gastrointestinal tract and have the potential to digest gluten polypeptides or breakdown gluten into non-immunogenic peptides (7,8).

Other strategies involve modulation of the gluten related inflammatory involvement of the small bowel mucosa by anti-IFN-γ, anti-TNF-α and anti-IL-15 agents (1,7). IL-15 is synthesized in the small intestine by antigen-presenting and epithelial cells. Moreover, it is regarded as the major factor involved in both IEL activation and proliferation, which are primarily CD8 lymphocites (9-11). The IEL are responsible for both enterocytes apoptosis and flattening of the villi, the main histopathologic characteristic in CD (2). Further, proinflammatory cytokine IL-15 has been recognized as relevant mediator in almost all pathophysiological processes of CD (2,3,9).

AMG 714 is a human immunoglobulin monoclonal antibody (IgG1κ) and inhibits the function of IL-15 and blocks IL-15-induced T cell proliferation (10), making it a plausible candidate for the treatment of CD (10-12).

Study on stage

In this issue of Lancet Gastroenterology and Hepatology, Lähdeaho *et al.* investigated the effects of the first anti IL-15 monoclonal antibody—AMG 714 for the treatment of patients with CD who underwent gluten challenge (9). The study is a prospective, controlled, randomized phase 2a trial which aims to evaluate both the efficacy and safety of AMG 714 (named PRV-015) 150 and 300 mg compared to placebo in adult CD. The patients were recruited from three clinical sites in Finland. Since patients on a GFD are likely to consume inadvertently variable amounts of gluten, the study protocol assumes that all the study subjects will have daily consumption of 2–4 g of gluten, according to subjective tolerance. This wise approach consented both the pathogenetic study of CD and the pharmacodynamics of AMG 714 in shorter time than would have been possible under real-life situation of inadvertent gluten assumption (9).

The inclusion criteria were a confirmed diagnosis of CD in adults between 18–80 years who had been adhering to a GFD for at least 12 months before inclusion in the study, CD-compatible HLA-DQ genotype (DQ2/DQ8), body-mass index of 16–45 kg/m^2, extensive blood-work to assess general health parameters, and , negative anti-tTG IgA suggestive of compliance to GFD) and negative Helicobacter Pylori testing. Patients were not considered for the study in case of CD related complications such as GFD refractory CD, enteropathy associated T-cell lymphoma, ulcerative jejunitis or if they show features of comorbid diverse immune disease, dermatitis herpetiformis, and CD gastro-intestinal symptom rating scale (CeD GSRS) score of more than 2 (9). Sixty-four patients were randomized to either the 150 mg AMG 714 group (n=22), the 300 mg AMG 714 group (n=22) or the placebo group (n=20). Stool consistency was recorded daily from basal assessment to week 16 by the Bristol stool form scale (BSFS), Anti-tTG and anti-DGP antibodies were analyzed monthly, and patients receiving AMG 714 were tested for antidrug antibodies using a bridging immunoassay. Patient-reported outcomes were recorded by an electronic home diary and four duodenal biopsy specimens per patient were obtained endoscopically at run-in and week 12 (9). The primary endpoint was the percentage change from baseline to week 12 in villous height-to-crypt depth (VHCD) ratio. Secondary endpoints were CD3-positive IEL density; subjective complains as measured by gastrointestinal symptom rating scale (GSRS), and BSFS plus changes in anti-tTG and anti-DGP antibodies from basal evaluation. Drug related side-effects were searched for in all subjects assuming at least one dose of study drug. The study failed to meet its primary outcome for the change in VHCD ratio was not significantly different between placebo and AMG 714,150 mg or between placebo and AMG 714,300 mg. However, patients in the higher schedule AMG 714 had better outcomes on intraepithelial lymphocyte density. In addition, patient reported that both symptom score and

fecal consistency were decreased suggesting global clinical improvement.

Neutralising antibodies were not evidenced on repeated blood sampling and no difference was reported between study drug and placebo groups at to the effects on anti-tTG IgA (9). A non-significant increment in body weight in the drug study group was an add on point to clinical benefit potentially due to improved nutrient absorption. However, bodyweight was not defined as an efficacy endpoint; thus, no statistical comparison was made between groups regarding bodyweight and nutrition state. A major strength of the study was given by an exclusive methodological component: the single blind diet advise of gluten-free cookies before initiating gluten challenge. In this manner, researchers could figure out clinical worsening due to the nocebo effect. The use of stool and urine sampling to test for gluten assumption, consideration of the nocebo effect, and the central preparation and reading of biopsy samples to reduce variability in histology reports and IEL count emphasize the trial novelty.

Expert conclusion

Notwithstanding the failure of the primary endpoint, benefits observed in the group of subjects undergoing gluten challenge suggest that 300 mg AMG 714 given every 2 weeks might improve both disordered histology and symptoms due to gluten exposure. In addition, an improvement in both patient-reported and physician-assessed outcomes was reported in the drug study group compared to the placebo group (9).

Compliance to treatment in the AMG 714 group was optimal and no relevant side effects were reported. Frequency of mild adverse events, mostly infections, was similar between drug study and placebo groups (9). Small sample size, short study duration and lack of a standardized assay to precisely sample for IL-15 concentrations in blood and tissues in the presence of an anti-IL-15 antibody were the main limitations of the study. Moreover, a selection bias could not be excluded and a larger sample of CD patients studied for an extended time interval is warranted to rehearse the positive findings. In conclusion, the study support the role of gluten induced inflammatory activation as relevant etiology of celiac disease. Modulation of the inflammation seems a promising target to improve GFD outcome in celiac disease and to ease diet adherence in this disabling disease. Additional studies are eagerly awaited to deepen and extend the findings of this cornerstone research to potentially have CD patients glimpse the light at the end of the GFD tunnel.

Footnote

References

1. Al-Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J 2019;7:583-613.
2. Parzanese I, Qehajaj D, Patrinicola F, et al. Celiac disease: From pathophysiology to treatment. World J Gastrointest Pathophysiol 2017;8:27-38.
3. De Marchi S, Chiarioni G, Prior M, Arosio E. Young adults with coeliac disease may be at increased risk of early atherosclerosis. Aliment Pharmacol Ther 2013;38:162-9.
4. King JA, Jeong J, Underwood FE, et al. Incidence of Celiac Disease Is Increasing Over Time: A Systematic Review and Meta-analysis. Am J Gastroenterol 2020;115:507-25.

5. Popa SL, Chiarioni G, David L, et al. Functional Emesis. J Gastrointestin Liver Dis 2019;28:319-25.
6. Itzlinger A, Branchi F, Elli L, et al. Gluten-Free Diet in Celiac Disease—Forever and for All? Nutrients 2018;10:1796.
7. Sharma N, Bhatia S, Chunduri V, et al. Pathogenesis of Celiac Disease and Other Gluten Related Disorders in Wheat and Strategies for Mitigating Them. Front Nutr 2020;7:6.
8. Cinova J, De Palma G, Stepankova R, et al. Role of intestinal bacteria in gliadin-induced changes in intestinal mucosa: study in germ-free rats. PLoS One 2011;6:e16169.
9. Lähdeaho ML, Scheinin M, Vuotikka P. 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;4:948-59.
10. Lebrec H, Horner MJ, Gorski KS, et al. Homeostasis of human NK cells is not IL-15 dependent. J Immunol 2013;191:5551-8.
11. Giuffrida P, Di Sabatino A. MicroRNAs in Celiac Disease Diagnosis: A miR Curiosity or Game-Changer? Dig Dis Sci 2020;65:1877-9.
12. Charlesworth RP. Diagnosing coeliac disease: Out with the old and in with the new? World J Gastroenterol 2020;26:1-10.