International Journal of Celiac Disease, 2018, Vol. 6, No. 2, 33-36
Available online at http://pubs.sciepub.com/ijcd/6/2/8

DOI:10.12691/ijcd-6-2-8

Celiac Disease Pipeline: An Examination of New Treatment Options Currently Under Investigation

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Abstract Celiac disease is a chronic gastrointestinal autoimmune disease that occurs in approximately 0.5-1% of the U.S. population. At this point in time there is no cure nor therapeutic option available for patients with CD. The only treatment option is a 100% strict adherence to a gluten free diet. However, even complete adherence may not be enough as some foods might contain cross contaminated gluten. The purpose of this study was to analyze and describe different therapy options currently being investigated for potential use in patients with CD. An analysis of ClinicalTrials.gov was performed with the search term "Celiac Disease". The search returned 192 results, however only 8 were pharmacologic treatment options. The pharmacologic therapies located were TIMP-GLIA, ALV003, AMG714, pancrelipase, Nexvax2, RO5459072, Hu-Mik Beta-1, and Necator americanus (Na). With the nonexistent treatment options currently available, further research needs to be completed to create new therapeutic options for patients with CD with the goal of ultimately curing patients.

Keywords: *celiac disease, pharmaceuticals, clinical trials, treatment*

Cite This Article: Eric P. Borrelli Pharm D, "Celiac Disease Pipeline: An Examination of New Treatment Options Currently Under Investigation." *International Journal of Celiac Disease*, vol. 6, no. 2 (2018): 33-36. doi: 10.12691/ijcd-6-2-8.

1. Introduction

Celiac disease (CD) is a gastrointestinal (GI) autoimmune disease that occurs in approximately 0.5-1% of the population in the United States [1,2]. Complications and adverse effects of CD can lead to a decrease in quality of life for patients. At this point in time there is no cure for CD. There are also zero medications approved by the Food and Drug Administration (FDA) with an indication for treatment of CD. The only treatment option for patients is strict adherence to a 100% gluten free diet [3]. Considering that there are over 1,000,000 patients in the United States (U.S.) alone with CD, therapy options are needed for patients to treat CD and potentially help cure this disease.

Before any medication or therapeutic agent can make a difference in patients' lives, it must go through an extensive process of clinical trials and needs approval from the Food and Drug Administration (FDA). There are 4 different phases of clinical trials that medications go through, and the first 3 phases are needed to be completed in order for a medication to be approved and make it to market. Phase 1 trials are aimed at determining the safety of the medication as well as optimal dosing [4]. The trial drug is given to a small number of healthy patients and the dose is slowly titrated until a desired effect is met or side effects become too severe [4]. Phase 2 trials are aimed at determining preliminary evidence of efficacy of the medication as well as potential adverse effects [4]. Phase 2 trials last longer than phase 1 trials and have a larger sample population. Phase 3 trials are aimed at evaluating the safety and efficacy of the trial drug in a larger population [4]. Phase 3 trials are usually randomized and compared against a control group of either placebo or active medication. Phase 4 trials are considered postmarketing analysis and are undertaken to determine the effectiveness and safety profile of a medication under real-world settings after it has already been approved [4,5].

The purpose of this study is to analyze different therapy options currently under trial with the purpose of treating CD.

2. Methods

An analysis was performed of ClinicalTrials.Gov with the search term "Celiac Disease" to review and describe different therapy options that might come to market in the years to come. After locating the pharmacologic treatment options currently listed in ClinicalTrials.Gov, each treatment was further researched to help provide a description and inform readers of what options might be available on the market in the coming years. ClinicalTrials.Gov is run by the United States National Library of Medicine (NLM) at the National Institute of Health (NIH) and is the world's largest registry of clinical trials.

3. Results

The search of "Celiac Disease" on ClinicalTrials.Gov returned 192 studies. After analyzing the trials listed in the

database, 8 were for potential pharmacologic treatment therapies. The other trials listed were additional studies for the same drug therapy, dietary supplements, diagnostic testing, other, or nonapplicable. The pharmacologic therapies located were TIMP-GLIA, ALV003, AMG714, pancrelipase, Nexvax2, RO5459072, Hu-Mik Beta-1, and Necator americanus (Na).

3.1. TIMP-GLIA

TIMP-GLIA is a drug that is currently in Phase 1 that is given intravenously (IV). The trial, titled: "A Phase 1, First-in-Human, 2-Part, Multicenter Dose Escalation and Repeat Dose Study of the Safety, Tolerability and Pharmacokinetics of TIMP-GLIA in Subjects With Celiac Disease" {NCT03486990}, is an open label trial with an estimated 22 participants. The trial started in February 2018 and has an estimated completion date of March 2019.

3.2. ALV003

ALV003 is a combination product that contains two gluten specific proteases (ALV001 and ALV002). ALV001 is a modified recombinant proenzyme form of cysteine endoprotease which is derived from barley [6]. ALV002 is a modified recombinant form of prolyl endopeptidase from *Sphingomonas capsulate* [6]. These proteases work together to degrade gluten and work faster and more efficiently in combination versus either protease alone [7]. ALV003 has completed phase 2 trials. Results from 2 of the phase 2 trials (A Phase 2a, Double-Blind, Placebo Controlled Study of the Efficacy, Safety and Tolerability of 6-weeks Treatment With ALV003 In Patients With Well-Controlled Celiac Disease {NCT00959114}; and A Phase 2a, Double-Blind, Placebo Controlled Study of the Efficacy, Safety and Tolerability of 6-weeks Treatment With Varying Methods of ALV003 Administration in Patients With Well-Controlled Celiac Disease {NCT01255696}) indicate that ALV003 appears to alleviate gluten induced intestinal mucosal injury in patients with CD [6]. Another phase 2 trial (A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study of the Efficacy and Safety of ALV003 Treatment in Symptomatic Celiac Disease Patients Maintained on a Gluten-Free Diet {NCT01917630}) showed that seropositive CD patients had symptomatic improvements when taken with meals [8]. However, patients with symptomatic CD and duodenal mucosal injury did not have histological or symptomatic improvements compared to placebo [9].

3.3. AMG714

AMG714 is fully human anti-interleukin (IL)-15 monoclonal antibody that is administered subcutaneously (SQ). AMG714 has completed two phase 2a trials for CD titled "A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of AMG 714 in Adult Patients With Celiac Disease" {NCT02637141} and "A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of AMG 714 in Adult Patients With Type II Refractory Celiac Disease, an In Situ Small Bowel T Cell Lymphoma" {NCT02633020}. AMG 714 is a biologic product that is injected SQ every 2 weeks. Results from these trials have yet to be posted or published.

3.4. Pancrelipase

Pancrelipase are pancreatic enzymes derived for porcine lipases, proteases, and amylases that are currently available as a prescription product [10-14]. Pancrelipase has several different brand name formulations currently available on the market via prescription, such as Viokace, Creon, Zenpep, Pertyze, and Pancreaze to name a few [10-14]. Although these products all contain pancrelipase formulations, none of them are interchangeable. Pancrelipase products have FDA approved indications for pancreatic insufficiency due to cystic fibrosis, pancreatitis, or pancreatectomy [10-14]. These products are all oral formulations. The pancrelipase product, Viokace, is currently in Phase 4 trials with aspirations of an indication in CD. The title of the clinical trial is "Pilot Study of the Efficacy of Pancreatic Enzyme Supplementation for Symptom Control in Celiac Disease Not Responding to the Gluten Free Diet" {NCT02475369}. The study is estimating 40 participants and is projected to be completed by December 2019. The primary endpoint is reduction in GI symptoms.

3.5. Nexvax2

Nexvax2 is a peptide based, epitope specific immunotherapy that is administered intradermally (ID) via injection [15]. Nexvax2 is customized for patients that are positive for the human leukocyte antigen (HLA)-DQ2·5 gene [16]. This represents approximately 90% of patients with CD [17, 18]. Nexvax2 contains 3 synthetic peptides (NPL001, NPL002, NPL003) that each have 15 to 16 amino acids and have at least 5 HLA-DQ2·5 restricted epitopes that are commonly recognized by gluten-reactive cluster of differentiation 4 (CD4) positive T cells [15, 16]. Nexvax2 completed a phase 1 trial in Australia titled "A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability of Nexvax2 Preceded by a Dose Titration Period in Subjects With Celiac Disease Currently on a Gluten-Free Diet" {NCT025828799}. The study included 38 participants with CD that are 5 HLA-DQ2·5 positive and were randomly assigned to a 1:1 ratio of either treatment or placebo. The treatment arm consisted of receiving Nexvax2 via ID injection twice weekly from 46 to 60 days consisting of 14 to 18 doses. The placebo arm consisted of receiving an ID injection of sodium chloride 0.9% twice weekly for 46 to 60 days consisting of 14 to 18 injections. The trial indicated that Nexvax2 could be administered safely in patients and showed trends of improved duodenal histology [16].

3.6. RO5459072

RO5459072 is an orally administered small molecule product that is a competitive inhibitor of the active site of cathepsin S [19]. RO5459072 completed a phase 1 trial titled "A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Parallel Study to Investigate the Pharmacokinetics, Pharmacodynamic Effects, Safety and

Tolerability of Repeated Dosing of RO5459072 in Volunteers With Celiac Disease" {NCT02679014}. 19 patients with CD on a gluten free diet and had HLA-DQ2.5 and HLA-DQ8 haplotypes were enrolled in the study. Patients were enrolled in a 1:1 ratio of treatment versus placebo. The treatment arm received 100mg of RO5459072 twice daily for 28 days with food with the exception of mornings of Days 7 and 21 in which the drug was given while fasting. The results of this trial have yet to be published.

3.7. Hu-Mik Beta-1

Hu-Mik Beta-1 is a monoclonal antibody that targets the cytokine receptor subunit IL-2/IL-15Rβ (CD122) as well as blocks IL-15 transpresentation [20]. Hu-Mik Beta-1 is in an open label, phase 1 clinical trial titled "Phase I Study of the Humanized Mik-Beta-1 Monoclonal Antibody Directed Toward IL-2/IL-15R Beta (CD122) That Blocks IL-15 Action In Patients With Refractory Celiac Disease" {NCT01893775}. The estimated enrollment for the study is 12 patients with all participants in the treatment arm. The patients will receive one dose of Hu-Mik Beta-1 every 3 weeks for 3 doses. This phase 1 study is still ongoing and the results have yet to be published.

3.8. Necator Americanus (Na)

Necator americanus (Na) is a hookworm that has been shown to alter the systemic and local immune makeup of the infected host [21]. The hookworm Na completed a blinded phase 2 trial titled "A Phase 2a, Randomized, Double Blinded, Placebo Controlled, Study Evaluating Immunity and Gluten-sensitivity by Inoculating Celiac Disease Patients With the Human Hookworm Necator Americanus" {NCT00671138}. There is also a phase 1 study currently in process as well as an additional phase 1 study that has already been completed using Na in CD. Twenty participants were randomized in a 1:1 ratio of treatment versus placebo. The treatment arm were inoculated with 10 Na larvae at week 0 and then an additional 5 Na larvae at week 12.

4. Discussion

Although these treatment options are currently under trial, there is no guarantee that any of them will ultimately make it to market. Approximately only 11% of drugs that make it to clinical trials ultimately pass and become approved [22]. With the high number of patients in the United States and around the world with CD, there are numerous reasons for continued research into finding appropriate therapies to help treat or cure this disease. Since there are no treatments available, there is a large economic incentive for pharmaceutical companies to try and develop a therapy aimed at this indication. Bringing to market one of the first ever treatment therapies for a disease with millions of patients could generate significant revenue for pharmaceutical companies. If new therapies can decrease adverse symptoms and hospitalizations while increasing quality of life, they could offer a significant cost-effective opportunity, even if they carry a large sticker price. Decreasing adverse symptoms and increase quality of life can also increase societal production. This will be due to patients missing less days of work and be more productive, leading to significant societal benefit. The only available treatment for patients with CD is a strict 100% gluten free diet. However, even adhering to this fully may still not be enough to prevent adverse effects. Even if foods are gluten free, they might contain cross-contaminated gluten if it was not prepared separately from other gluten products. In addition to this, some prescription, over-the-counter (OTC), or dietary supplements may contain gluten which can lead to adverse events. The cost of a hospitalization in the United States for CD has typically ranged between $9,500 to $11,500 [23]. Adhering to a strict gluten free diet also can be financially difficult for patients since gluten-free products tend to be significantly more expensive [24].

It is encouraging to see these 8 different products are currently being studied for their safety and efficacy in patients with CD. However, more research needs to be completed to try and find new therapies with novel mechanisms of action (MOA) with the hope of improving or preventing symptoms, treating the disease, and one day possibly curing CD.

5. Conclusion

There are currently several therapeutic options currently being investigated for treatment of CD. With the nonexistent treatment options currently available, further research needs to be completed to create new therapeutic options for patients with CD with the goal of ultimately curing patients.

Abbreviations

CD: Celiac Disease
GI: Gastrointestinal
FDA: Food and Drug Administration
U.S.: United States
NLM: National Library of Medicine
NIH: National Institute of Health
Na: Necator americanus
IV: Intravenous
ID: Intradermally
IL: Interleukin
SQ: Subcutaneously
HLA: Human leukocyte antigen
CD4: Cluster of differentiation 4
OTC: Over-the-counter
MOA: Mechanism of Action

Acknowledgements

No specific acknowledgements.

Conflict of Interest

The author has no conflicts of interest to disclose.

References

[1] Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012 Oct; 107(10): 1538-44.

[2] Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, Elitsur Y, Green PH, Guandalini S, Hill ID, Pietzak M, Ventura A, Thorpe M, Kryszak D, Fornaroli F, Wasserman SS, Murray JA, Horvath K. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003 Feb 10; 163(3): 286-92.

[3] Chou R, Bougatsos C, Blazina I, Mackey K, Grusing S, Selph S. Screening for Celiac Disease: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2017 Mar 28; 317(12): 1258-1268.

[4] Nguyen V, Sweet BV, Macek T. Defining the phases of clinical trials. Am J Health Syst Pharm. 2006 Apr 15;63(8):710-1.

[5] Rados C. Inside clinical trials: testing medical products in people. FDA Consum. 2003; 37(5): 30-5.

[6] Lähdeaho ML, Kaukinen K, Laurila K, et al. Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease. Gastroenterology. 2014 Jun; 146(7): 1649-58.

[7] Gass, J., Bethune, M., Siegel, M. et al. Combination enzyme therapy for gastric digestion of dietary gluten in patients with celiac sprue. *Gastroenterology*. 2007; 133: 472-480.

[8] Syage JA, Murray JA, Green PHR, Khosla C. Latiglutenase Improves Symptoms in Seropositive Celiac Disease Patients While on a Gluten-Free Diet. Dig Dis Sci. 2017 Sep; 62(9): 2428-2432.

[9] Murray JA, Kelly CP, Green PHR, Marcantonio A, Wu TT, Mäki M, Adelman DC; CeliAction Study Group of Investigators. No Difference Between Latiglutenase and Placebo in Reducing Villous Atrophy or Improving Symptoms in Patients With Symptomatic Celiac Disease. Gastroenterology. 2017 Mar; 152(4): 787-798. e2.

[10] Viokace (pancrelipase) [package insert]. Allergan Inc., Irvine, CA; 2017.

[11] Creon (pancrelipase) [package insert]. Abbott Laboratories, North Chicago, IL; 2012.

[12] Zenpep (pancrelipase) [package insert]. Aptalis Pharma US, Inc., Bridgewater, NJ; 2014.

[13] Pertyze (pancrelipase) [package insert]. Digestive Care, Inc., Bethlehem, PA; 2017.

[14] Pancreaze (pancrelipase) [package insert]. Janssen Pharmaceuticals, Inc., Titusville, NJ; 2018.

[15] Goel G., King T., Daveson A.J., et al. Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: two randomised, double-blind, placebo-controlled phase 1 studies. Lancet Gastroenterol. Hepatol. 2017; 2: 479-493.

[16] 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.

[17] Karell K., Louka A.S., Moodie S.J., et al. European Genetics Cluster on Celiac Disease HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. Hum. Immunol. 2003; 64: 469-477.

[18] Anderson R.P., Jabri B. Vaccine against autoimmune disease: antigen-specific immunotherapy. Curr. Opin. Immunol. 2013; 25: 410-417

[19] Theron M, Bentley D, Nagel S, et al. Pharmacodynamic Monitoring of RO5459072, a Small Molecule Inhibitor of Cathepsin S. *Frontiers in Immunology*. 2017; 8: 806.

[20] Waldmann TA. The biology of IL-15: implications for cancer therapy and the treatment of autoimmune disorders. J Investig Dermatol Symp Proc. 2013 Dec; 16(1): S28-30.

[21] Daveson AJ, Jones DM, Gaze S, et al. Effect of Hookworm Infection on Wheat Challenge in Celiac Disease – A Randomised Double-Blinded Placebo Controlled Trial. Gluud LL, ed. *PLoS ONE*. 2011; 6(3): e17366.

[22] Howland RH. How are drugs approved? Part 1: the evolution of the Food and Drug Administration. J Psychosoc Nurs Ment Health Serv. 2008 Jan; 46(1): 15-9.

[23] Borrelli EP. Trends in Hospitalizations for Celiac Disease in the United States. International Journal of Celiac Disease. 2017 Nov; 5(4): 150-154.

[24] Abdulla A, Garemo M. High cost of gluten free products might be challenging for people with celiac disease in the United Arab Emirates. 2018 May; 6(2): ahead of print.