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Celiac Disease Vaccination: Expectations and Reality

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Editorial

Celiac disease (CD) is a condition with a strong genetic predisposition that may affect people of all ages and gender. The established prevalence of the disease varies from 1:70 (in Australia) to 1:120 in Europe [1]. However, about 80% of the affected people remain undiagnosed. The main features of the disease are inflamed and flattened intestinal mucosa leading to small bowel damage [1]. Although CD is considered as an autoimmune disease characterized by sensitiveness to gluten throughout the whole life, thus, in this sense patients are never cured, even though a strict gluten-free diet (GFD) allows CD to be managed effectively [2]. The pathophysiology of CD remains elusive, although a substantial progress in the knowledge of gluten sensitization and the role of some environmental factors was made.

Currently, there is no FDA-approved therapeutic for the treatment of CD. Recently, a breakthrough was made by creating of vaccine for CD patients, similar to injection of insulin for diabetes, which promises to treat definitely patients with the disease. The Nexvax2 development received more than $40 million in financing in 2017 to fund further research. Chronologically, Biotech company initiates clinical trials for CD vaccine in 2012, then a year later, epitope-specific immunotherapy for CD announced the potential of vaccines against other autoimmune diseases. In 2016 and 2017 the search for CD vaccine got closer, as well as a study of new treatment for CD using nanoparticles began [3].

The CD vaccine is a form of immunotherapy, a promising approach where a small amount of the vaccine is given at first and the amount gradually increased, aiming patients that possess HLA-DQ2.5 to build up resistance to the gluten-avoiding any negative effects. However, Nexvax2 falls into the therapeutic category of vaccines and would be used along with the GFD. The underlying concept is to reprogram the immune system to learn not to react again gluten, thus, to stimulate immune tolerance towards gluten [3].

First investigations by Cour`s Pharmaceuticals were denoted to animal models of CD, by encapsulating fragments of gliadin folded in patented nanoparticles. In CD, these fragments pass through the intestinal wall and activate the immune response, which is the fundamental cause of the disease, leading to inflammation and intestinal villous atrophy. In contrast, by delivering them in the bloodstream *via* a single intravenous dose, gliadin is introduced to the immune system as a normal part of the diet. The fine mechanisms include reprograming the T-cells responsible for the symptoms of CD to stop triggering a pro-inflammatory response. This process leads to inducing immune tolerance. The therapy for CD patients on the base of these nanoparticles, called TIMP-GLIA then was used as a treatment in a clinical trial investigating [4].

The Phase I trial evaluated the safety, tolerability, and bioactivity of the vaccine was undertaken in Melbourne, Australia. The vaccine consisted of three specific peptides in gluten, identified by the immunologist Dr. Bob Anderson, as toxic to people with CD. The Phase I showed a good biological response to these peptides, and satisfying safe and tolerate profile of the vaccine. According to Dr. Anderson, more than 90% of the patients with the DQ2 genetic form of the disease could be influenced positively by the vaccine [4]. Phase I trial of Nexvax2-specific T-cell response confirmed the desired bioactivity in HLA-DQ2 genotype patients. The design of the study evaluated the effect of weekly injections of the vaccine over the CD patients on strict GFD for three weeks. The investigators suggested that the vaccine uses the correct peptides for establishing atolerate towards gluten, especially at the highest doses [4].

The randomized Phase II clinical trial will aim to demonstrate clinically relevant proof of concept for patients receiving a gluten challenge in an adjunct to a GFD, again in CD patients who possess HLA-DQ2.5 alleles. Approximately 90% of CD patients carry this immune recognition gene, which is the target of Nexvax2. In this way, Nexvax2 is the sole vaccine for CD in clinical development today. The aim of the proposed therapeutic approach is to protect patients with CD against inadvertent exposure to gluten [4]. In conclusion, the world's first potential vaccine for CD has shown promising results for treating the disease. Now we are expecting the results from Phase II trials within the next year.

Dr. Steven Gillis, a trained immunologist and a credited pioneer in the field of cytokines and cytokine receptors, is looking forward to exploiting the potential of so-called Epitope-Specific Immuno-Therapy (ESIT) platform in the clinic. Having in mind that approximately 30% of patients with CD have other autoimmune diseases such as type 1 diabetes and thyroid disease, the investigators aim to develop new therapies that could benefit patients beyond those living with CD [5].

Dr. Anderson suggests another role of the investigated to improve diagnostic testing of the CD. Diagnosing CD relies on biopsy testing which can be quite costly and invasive tests and to confirm the disease. According to him, the results of a population study suggest that a combination of blood and genetic testing could effectively diagnose CD with up to 50% reduction in invasive tests and costs as well [5]. Immusan T, collaborating with INOVA Diagnostics, develop improved serologic tests for CD, including functional T-cell diagnostic methods, designed to be used both as a standalone test as well as a monitoring test for Nexvax2 [6].

Concerns

As every novel therapy approach, vaccine treatment for CD has its concerns. Although promising results from Phase I of the clinical trial,

Phase II may provide surprises. The immune tolerance is desirable but it is difficult to be reached.

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