A Phase I study to determine safety, tolerability and bioactivity of Nexvax2® in HLA DQ2+ volunteers with celiac disease following a long-term, strict gluten-free diet

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Introduction

Discovery of the immunodominant T-cell stimulatory peptides in gluten enables development of highly specific diagnostics and therapeutics that target pathogenic T cells in celiac disease (1).

Recently, we showed that the majority of gluten-specific T cells circulating in blood after oral wheat, barley or rye challenge recognize one of three deamidated peptides derived from wheat α-gliadin (NPL001: pLQEFQPOELPYPQPO-amide), wheat ω-gliadin/barley C-hordein (NPL002: pLQEFQPOELPYPQPO-amide), and from barley B-hordein (NPL003: pLQEFQPOELPYPQPO-amide). These three peptides include at least five largely distinct HLA DQ2-restricted epitopes: DQ2-α-i (pLQEFQPOELPYPQPO), DQ2-α-II (pLQEFQPOELPYPQPO), DQ2-ω-I (pLQEFQPOELPYPQPO), and DQ2-ω-II (pLQEFQPOELPYPQPO) (predicted sequence: PIPFEPQPO) that collectively are recognized by almost all of the 80% of celiac disease patients who possess HLA DQ2 (encoded by HLA DQA1*05 and HLA DQB1*02) but not HLA DQ8 (encoded by HLA DQA1*03 and HLA DQB1*0302) (2).

Celiac disease is the first human disease for which there is clear understanding of the peptides recognized by the pathogenic T cell population.

One application of this new knowledge in celiac disease is to design and test the potential for peptide-based immunotherapy since it may be capable of restoring immune tolerance to gluten and allow return to a normal diet. We have shown in a mouse model of HLA DQ2-restricted T cell immunity to the α-gliadin epitope DQ2-ω-I (pLQEFQPOELPYPQPO) that repeated dosing over 2–4wks with Nexvax2®, an equimolar mix of NPL001, NPL002 and NPL003 in saline, is safe and shifts the phenotype of T cells specific for NPL001 from proinflammatory to anergic and/or regulatory (3).

Having completed a preclinical development program with Nexvax2® manufactured to cGMP standards, we sought to test whether Nexvax2® was safe, tolerated and immunogenic in HLA DQ2+ volunteers with celiac disease following a strict gluten free diet.

Objectives

The primary objective of this study was to evaluate the safety and tolerability of weekly injections of Nexvax2® administered intra-d. (i.d.) for three weeks.

The secondary objective of this study was to compare the bioactivity of Nexvax2® in celiac disease volunteers through the measurement of T-cell response as assessed by T-cell frequency and cytokine release.

Methods

Diagnosis and main criteria for inclusion:
Healthy individuals with a diagnosis of celiac disease according to accepted European Society of Paediatric Gastroenterology, Hepatology and Nutrition diagnostic criteria, following a gluten free diet meeting Food Standards Australia New Zealand (FSANZ) criteria, who possessed both alleles encoding human leukocyte antigen (HLA) DQ2 (DQA1*05 and DQB1*02) but not either of those encoding HLA DQ8 (DQA1*03 and DQB1*02).

Nexvax2® for Injection contains equimolar amounts (0.159 micromole per 100 microlitres, approx. 3 mg/mL) of each NPL001, NPL002 and NPL003 in 0.9% normal saline sterile solution.

Subjects were randomized to receive either 9, 30, 60 or 90 μg of Nexvax2® or placebo i.d. weekly for 3 weeks.

The duration of the clinical phase of the study for each dose group (cohort) was 50 days, including a 30 days follow-up but not including Screening.

Results

SAFETY RESULTS:
Nexvax2® was well tolerated. The most commonly occurring adverse events were headaches and gastrointestinal disorders. Gastrointestinal adverse events similar to those caused by gluten ingestion in celiac disease were more commonly observed in subjects receiving 60 and 90 μg of Nexvax2® compared with 9 or 30 μg of Nexvax2® or placebo. For non-celiac symptoms, the incidence, relationships and severity of adverse events were similar between active and placebo subjects. There were no clinically relevant changes in safety laboratory parameters or vital signs observed in this study. One subject in the 90 μg Nexvax2® dosing cohort withdrew due to gastrointestinal symptoms graded severe. There were no deaths or serious adverse events.

Bioactivity of Nexvax2® in celiac disease volunteers was assessed through the measurement of gluten-specific T-cell frequency and cytokine release. Several subjects had positive interferon-γ (IFN-γ) enzyme-linked immunosorbent assay (ELISpot) responses subsequent to at least one dose of Nexvax2®. Positive responses in subjects randomised to receive Nexvax2® were most commonly observed on study Day 6.

Conclusions

These safety and preliminary immunogenicity data are supportive of further clinical evaluation of Nexvax2®.

The time course of symptoms and mobilization of gluten-specific T cells observed after administration of Nexvax2® were similar to those triggered by acute oral gluten exposure in HLA DQ2+ patients with celiac disease on GFD, suggesting a further potential role for Nexvax2® as a functional diagnostic.