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NDV-3, a recombinant alum-adjuvanted vaccine for *Candida* and *Staphylococcus aureus*, is safe and immunogenic in healthy adults

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ABSTRACT

The investigational vaccine, NDV-3, contains the N-terminal portion of the *Candida albicans* agglutinin-like sequence 3 protein (Als3p) formulated with an aluminum hydroxide adjuvant in phosphate-buffered saline. Preclinical studies demonstrated that the Als3p vaccine antigen protects mice from oropharyngeal, vaginal and intravenous challenge with *C. albicans* and other selected species of *Candida* as well as both intravenous challenge and skin and soft tissue infection with *Staphylococcus aureus*. The objectives of this first-in-human Phase I clinical trial were to evaluate the safety, tolerability and immunogenicity of NDV-3 at two different antigen levels compared to a saline placebo. Forty healthy, adult subjects were randomized to receive one dose of NDV-3 containing either 30 or 300 μg of Als3p, or placebo. NDV-3 at both dose levels was safe and generally well-tolerated. Anti-Als3p total IgG and IgA1 levels for both doses reached peak levels by day 14 post vaccination, with 100% seroconversion of all vaccinated subjects. On average, NDV-3 stimulated peripheral blood mononuclear cell (PBMC) production of both IFN-γ and IL-17A, which peaked at day 7 for subjects receiving the 300 μg dose and at day 28 for those receiving the 30 μg dose. Six months after receiving the first dose of NDV-3, nineteen subjects received a second dose of NDV-3 identical to their first dose to evaluate memory B- and T-cell immune responses. The second dose resulted in a significant boost of IgG and IgA1 titers in >70% of subjects, with the biggest impact in those receiving the 30 μg dose. A memory T-cell response was also noted for IFN-γ in almost all subjects and for IL-17A in the majority of subjects. These data support the continued investigation of NDV-3 as a vaccine candidate against *Candida* and *S. aureus* infections.

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1. Introduction

Candida sp. are a major cause of hospital acquired infections in the U.S. and worldwide [1,2]. *Candida* sp. are now equivalent to enterococci as the third most frequent hospital acquired bloodstream isolates [3,4], accounting for 10% of bloodstream infections and 11% of catheter-related infections [5]. Population-based surveys in the U.S. have reported the annual incidence of *Candida* bloodstream infections is approximately 20 cases per 100,000 people (60,000 cases per year) [6,7]. In high risk/hospitalized patients, this incidence increases 50-fold [1,6,8,9]. These rates represent 15 to 20-fold increases compared to two decades earlier [10–12]. In addition to hematogenously disseminated candidiasis, mucosal candidal infections are common and can be persistent in some patients, causing recurrent disease several times per year. Most notable in this respect is recurrent vulvovaginal candidiasis, which impacts 5–8% of women in the US [13].

Staphylococcus aureus is the most common cause of skin and skin structure infections [14] and endocarditis [5], and the second most common cause of bacteremia [3,4]. *S. aureus* is a primary cause of a variety of hospital acquired infections, including ventilator-associated pneumonia, intravenous-catheter associated infections, post-surgical wound infections and is also a predominant cause of battlefield wound infections [15,16]. This organism frequently causes invasive infections in neutropenic patients and those undergoing solid-organ or hematopoietic stem cell transplants [17].

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Invasive infections caused by *S. aureus* continue to increase in frequency [18,19]. The increase in incidence of serious infections caused by *S. aureus* is concerning given the high mortality associated with *S. aureus* bacteremia and endocarditis (15–40%), even with appropriate antimicrobial therapy [18,20,21]. In addition, over the past decade *S. aureus* has become increasingly resistant to available antimicrobials [22]. To date, there are no licensed prophylactic or therapeutic vaccines either for *S. aureus* or *Candida*.

The agglutinin-like sequence 3 protein (Als3p) of *C. albicans* is both an adhesin [23] and an invasin [24] for *Candida*. It also has both sequence and structural homology with cell surface proteins on *Staphylococcus aureus* [23]. These findings led to its evaluation as a vaccine antigen where it was demonstrated to have protective efficacy in preclinical animal models of oral, vaginal and disseminated candidiasis as well as disseminated staphylococcemia [25–27] and *S. aureus* skin and soft tissue infection (unpublished data). Additionally, this protective immunity was effective against several species of *Candida* [25] and against several clinical isolates of *S. aureus* [27]. Finally, the vaccine was shown to be highly immunogenic in animal models, inducing robust anti-Als3p B-cell response in mice [28], rabbits and non-human primates (unpublished data) along with robust T-cell responses in mice [29].

Based on these preclinical observations, purified Als3p bulk was manufactured under current Good Manufacturing Practices (cGMP), incorporated into formulations containing aluminum hydroxide as an adjuvant (designated as NDV-3 vaccine) and evaluated in this clinical study. The results of evaluating the safety, tolerability and immunogenicity of NDV-3 vaccine in healthy volunteers are presented below.

2. Methods

2.1. Study design

The study was a double-blind, placebo-controlled, ascending dose escalation study (30 and 300 μg) that enrolled healthy adults at a single study site. Vaccinations occurred on study day 0, with follow up evaluations on study days 3, 7, 14, 28, 90 and 180. A subset of vaccinees was re-consented to receive a second dose of vaccine on study day 180, with follow up visits 7, 14, and 90 days after the second dose. The lower participation rate in receiving the second dose (9 of 15 for the 30 μg dose and 10 of 15 for the 300 μg dose) was documented as primarily due to the timing of the second dose and follow-up conflicting with mid-summer personal schedules. Details of the study design and execution are provided in Supplemental Materials.

2.2. Vaccine and adjuvants

The active component of the NDV-3 vaccine is a recombinant version of the N-terminal region (416 amino acids) of the *C. albicans* Als3p with the addition of a six-His tag and linker sequences [26]. Als3p was produced by batch fermentation of a *Saccharomyces cerevisiae* expression cell line at 100 L scale, harvested by centrifugation and purified using two chromatography columns (nickel-affinity and hydrophobic interaction resins) followed by concentration, diafiltration into phosphate-buffered saline (PBS), pH 7, and filtration. The purified Als3p bulk drug substance was intact, monomeric and 99% pure by SDS-PAGE with Coomassie staining and was formulated with aluminum hydroxide at 1.0 mg Al/mL in PBS, pH 7. Two final container vaccine clinical lots were used for this study; lot 0939 (60 μg Als3p/mL) and lot 0940 (600 μg Als3p/mL). Clinical lots were stored at 2–8 °C post manufacture and monitored for stability. Manufacture of the bulk drug substance and final container lots using cGMPs was conducted by Althea Technologies (San Diego, CA).

2.3. Immunogenicity analysis

Blood samples were obtained from subjects on the specified days post vaccination. Plasma and PBMCs were isolated using standardized procedures. Plasma samples were evaluated for anti-Als3 total IgG and for anti-Als3 IgA1 by standardized ELISA methodology. Results are expressed in units of dilution^{-1}. PBMCs were evaluated by ELISpot analysis to determine the portion of cells that could be stimulated to produce IFN-γ or IL-17A (two separate assays). Results are expressed in units of spot forming units (SFU) per 10^6 cells. Details of the above procedures are provided in Supplemental Materials.

2.4. Statistical analyses

Statistical analysis of assay results used non-parametric analysis using the Wilcoxon rank-sum test [30]. Evaluation of trends across groups used the Kruskal–Wallis test [31].

3. Results

An overview of the clinical study design (Fig. S1) and execution (Table S1) are provided in Supplemental Materials.

3.1. Safety

In this study population, NDV-3 was safe and generally well-tolerated after one or two doses. Local injection site reactions to placebo (post dose 1) and vaccine and (post dose 1 and 2) are summarized in Table 1. The most common complaint was injection site pain, typically mild, lasting 1–2 days after vaccination and resolving within 2–3 days without sequelae.

The systemic and injection site adverse events (AEs) occurring in at least two study subjects after either the first or the second dose are presented in Table 1. After dose 1 each of the systemic AEs shown in Table 1 were reflected in ≥2 of the 40 subjects. After dose 2, the most common systemic AEs were fatigue and headache (5 out of 19 (26%) subjects for each). Systemic AEs were usually mild and occasionally moderate, but all resolved without sequelae within a few days. There were no notable differences in systemic AEs between the two dose levels.

3.2. Immune response

Plasma Anti-Als3p Total IgG and IgA1. Prior to vaccination (day 0), 36 of the 40 subjects exhibited a detectable pre-existing anti-Als3p total IgG titer ranging from 114 to 2608 dilution^{-1}, with 4 subjects showing IgG titers below the limit of detection (LOD) of the assay (<50 dilution^{-1}). For IgA1 titers, 36 of the 40 subjects exhibited pre-existing detectable anti-Als3p IgA1 titer ranging from 102 to 6473 dilution^{-1}, with 4 subjects showing IgA1 titers below the LOD (<50 dilution^{-1}). Two subjects had no detectable anti-Als3p IgG or IgA1 prior to vaccination.

The geometric mean of anti-Als3p total IgG titers (Fig. 1A) and IgA1 titers (Fig. 1B) rose quickly after the first dose of vaccine, showing a substantial rise by day 7 post vaccination and reaching a maximum by day 14 post vaccination. The IgG and IgA1 titers from day 7 on were significantly higher for the 300 μg dose relative to the 30 μg dose (Mann–Whitney test, $p < 0.05$) and both were beyond the range of placebo recipient titers (Mann–Whitney test, $p < 0.001$). Antibody titers out to 180 days post vaccination showed roughly a two-fold decline from the maximum titers.

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