Vaccine 32 (2014) 6469–6477

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Immunogenicity and safety of Advax™, a novel polysaccharide adjuvant based on delta inulin, when formulated with hepatitis B surface antigen: A randomized controlled Phase 1 study

David Gordon[a], Peter Kelley[a], Susanne Heinzel[b], Peter Cooper[b,d,e], Nikolai Petrovsky[b,c,*]

[a] Department of Microbiology and Infectious Diseases, Flinders Medical Centre/Flinders University, Adelaide 5042, Australia
[b] Vaxine Pty Ltd, Bedford Park, Adelaide 5042, Australia
[c] Department of Endocrinology, Flinders Medical Centre/Flinders University, Adelaide 5042, Australia
[d] Cancer Research Laboratory, Australian National University Medical School at The Canberra Hospital, Garran, ACT 2605, Australia
[e] John Curtin School of Medical Research, Australian National University, Acton, ACT 2601, Australia

ARTICLE INFO

Article history:
Received 23 July 2014
Received in revised form
15 September 2014
Accepted 17 September 2014
Available online 27 September 2014

Keywords:
Hepatitis B
Vaccine
Adjuvant
Clinical trial
Human
Phase 1
Delta inulin
Advax

ABSTRACT

There is a need for additional safe and effective human vaccine adjuvants. Advax™ is a novel adjuvant produced from semi-crystalline particles of delta inulin. In animal studies Advax enhanced humoral and cellular immunity to hepatitis B surface antigen (HBsAg) without inducing local or systemic reactogenicity. This first-in-man Phase 1 clinical trial tested the safety and tolerability of three intramuscular doses of HBsAg formulated with Advax in a group of healthy adult subjects. Advax was well tolerated with injection site pain scores not significantly different to subjects receiving HBsAg alone and no adverse events were reported in subjects that received Advax. Seroprotection and HBsAb geometric mean titers (GMT) after three immunizations were higher in the Advax 5 mg (seroprotection 5/6, 83.3%, GMT 40.7, 95% CI 11.9–139.1) and 10 mg (seroprotection 4/5, 80%, GMT 51.6, 95% CI 10.0–266.2) groups versus HBsAg alone (seroprotection 1/5, 20%, GMT 4.1, 95% CI 1.3–12.8). Similarly the proportion of subjects with positive CD4 T-cell responses to HBsAg was higher in the Advax 5 mg (4/6, 67%) and Advax 10 mg (4/5, 80%) groups versus HBsAg alone (1/5, 20%). These results confirm the safety, tolerability and immunogenicity of Advax adjuvant observed in preclinical studies. Advax may represent a suitable replacement for alum adjuvants in prophylactic human vaccines subject to confirmation of current results in larger studies. Australia and New Zealand Clinical Trial Registry: ACTRN12607000598482.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

Hepatitis B virus (HBV) is the commonest cause of chronic liver infection and can lead to cirrhosis and liver cancer. Chronic infection most commonly affects infants after maternal transmission. In Africa and Asia, up to 10% of the population have chronic HBV infections with an estimated 240 million individuals globally being chronic carriers and >780,000 dying from liver failure each year [1].

Prophylactic immunization with plasma-purified inactivated HBV or yeast-expressed recombinant hepatitis B surface antigen (HBsAg) largely prevents clinical HBV infection [2]. HBsAg by itself is poorly immunogenic and therefore requires an adjuvant to be effective [3,4]. Traditionally, aluminum hydroxide or aluminum phosphate (collectively known as alum) have been used to adjuvant HBV vaccines. Immunization of children with alum-based prophylactic HBV vaccines is 90–95% effective in preventing chronic HBV infection [3]. However, individuals over 40 years of age or with immunodeficiency, diabetes mellitus or renal impairment have suboptimal responses to alum-based vaccines [5]. There is also a need for therapeutic vaccines for those with chronic HBV infection, with alum-based HBV vaccines being ineffective in this context [6]. Attempts to improve HBV vaccine potency for poor responder populations have included use of double-dose HBsAg vaccines [7], use of preS antigens [8] and use of alternative adjuvants such as AS04, a combination of alum and monophosphoryl lipid A (Fendrix®, GlaxoSmithKline, UK) approved in Europe for renal hemodialysis patients [9,10] and an immunostimulatory oligonucleotide adjuvant (Heplisav®, Dynavax, USA) in clinical development in the US [11,12].

Advax™ is a novel adjuvant produced from microparticles of delta inulin (β-D-(2 → 1)-polyfructofuranosyl-D-glucose) [13].

* Corresponding author at: Department of Diabetes and Endocrinology, Flinders Medical Centre/Flinders University, Bedford Park, SA 5042, Australia.
Tel.: +61 8 82044572; fax: +61 8 82045987.
E-mail address: nikolai.petrovsky@flinders.edu.au (N. Petrovsky).

http://dx.doi.org/10.1016/j.vaccine.2014.09.034
0264-410X/© 2014 Elsevier Ltd. All rights reserved.

Advax arose from research showing that the normally water soluble plant-derived polysaccharide inulin, is capable of crystallizing into a series of polymorphic forms distinguished by progressively higher temperatures of solubility [14] due to repeated addition of a crystal unit cell [15]. Delta inulin is distinguished from earlier described inulin isoforms (alpha, beta and gamma) by being relatively insoluble at mammalian body temperature bestowing it with unique immunological properties including potent adjuvant properties, not exhibited by more soluble inulin forms. In animal studies, Advax enhanced adaptive immune responses to a wide variety of viral and bacterial antigens including influenza [16,17], Japanese encephalitis [18,19], West Nile virus [20], HIV [21] and anthrax vaccines [22]. Mice immunized with HBsAg with Advax exhibited enhanced HBsAb titers along with antigen dose-sparing and enhanced cellular immune responses including CD4 and CD8 T-cell proliferation and Th1, Th2 and Th17 cytokine production [23]. The favorable effects of Advax on HBsAg immune responses were similarly evident in guinea pigs [23]. A notable finding in all animal studies conducted of Advax to date has been the lack of local or systemic reactogenicity.

This Phase 1 study was conducted to confirm safety and tolerability of Advax adjuvant in healthy adult subjects, as a prerequisite for subsequent trials to test its efficacy in poor responder populations. A secondary objective was to assess the ability of Advax to enhance the human immune response against HBsAg. As shown below, Advax was well tolerated and no safety issues were identified. When compared to HBsAg alone, formulation with Advax enhanced HBsAb titers and T-cell responses, consistent with it being an effective human adjuvant.

2. Methods

2.1. Study design

The study was a single center, randomized, observer and participant blinded, controlled Phase 1 trial conducted at Flinders Medical Centre in Adelaide, Australia. The study was conducted under the Clinical Trial Notification (CTN) provisions of the Australian Therapeutic Goods Administration, after approval by the Southern Adelaide Human Research Ethics Committee. Under the CTN process the TGA delegates responsibility for approval of a clinical trial to the Institutional Ethics Committee. After providing informed consent and being assessed for eligibility, subjects were examined and blood taken for safety analysis and measurement of baseline HBsAb titers. Eligible subjects were randomized using an on-line tool (www.randomiser.com) to receive an accelerated immunization course of three intramuscular doses a month apart of HBsAg (Butantan Institute, Brazil) alone or with Advax, 5 mg or 10 mg. This vaccine regimen was chosen for convenience and differed slightly from the usual administration course in Brazil of the alum-adjuvanted Butantan vaccine which is administered at 0, 1, and 3 months [24]. Randomization codes were loaded into numbered sealed envelopes sequentially opened by clinical staff to allocate subjects to study groups. On post-immunization days 1 and 7, subjects returned to the clinic for inspection of the vaccination site by a blinded observer and to have their diary reviewed. A month after each immunization subjects returned to have blood taken for HBsAb titers. The efficacy endpoint was frequency of seroprotection (HBsAb >10 mIU/mL) 1 month after the final vaccine dose. Injection site pain was assessed by visual analog pain scores (VAPS) and safety was assessed by the frequency of local and systemic solicited and unsolicited adverse events. Blood samples were obtained at each visit for additional safety assessments.

2.2. Enrolment criteria

The study population comprised healthy adults aged 18–40 years without evidence of prior HBV infection or HBV immunization. Exclusion criteria included, immunodeficiency, diabetes mellitus, significant liver disease, significant kidney disease, any serious systemic illness in the last 6 months, history of vaccine allergy, women of childbearing potential unless using a reliable and appropriate contraceptive method, pregnant or lactating women, concurrent immunosuppressive therapy, including corticosteroids (with the exception of topically applied/inhaled steroids), known infection of human immunodeficiency virus (HIV), history of intravenous drug abuse or alcohol abuse or clinically-significant abnormal baseline blood count.

2.3. Study vaccines

Current Good Manufacturing Practices (cGMP) recombinant HBsAg produced in *Hansenula polymorpha* was a gift of Butantan Institute, Sao Paulo, Brazil. It is a component of a licensed Brazilian vaccine formulated with alum adjuvant [24]. Each subject received 7 μg HBsAg alone or combined with Advax 5 mg or 10 mg. Alum-adjuvanted HBsAg vaccines typically contain 10–20 μg HBsAg [24], and a 7 μg dose was chosen for this study to set a stringent benchmark and test whether the adjuvant could compensate for this lower antigen dose. Advax adjuvant (Vaxine Pty Ltd, Adelaide, Australia) manufactured under Good Laboratory Practices (GLP) was supplied as a sterile suspension of delta inulin microparticles in a bicarbonate buffer. Each vaccine was injected in a final volume of 0.5 mL with Advax adjuvant formulated with HBsAg immediately prior to immunization by intramuscular injection into the deltoid muscle of the non-dominant arm. We have previously shown that unlike alum adjuvant, Advax does not absorb HBsAg. In animal studies injection of Advax adjuvant 24 h before HBsAg still potentiated the antibody response [23]. Hence antigen absorption and depot formation does not appear necessary for Advax's action.

2.4. HBsAb assay

HBsAb titers were measured in serum separated from venous blood collected into Z Serum Separator Clot Activator Vacuette tubes (Greiner Bio-one) using a commercial AxSYM AUSAB assay (Abbott Diagnostics), following the manufacturer's protocol.

2.5. CD4+ T-cell proliferation assay

Peripheral blood mononuclear cells (PBMC) were isolated from venous blood using BD Vacutainer CPT cell preparation tubes. Proliferation was measured using a carboxyfluorescein succinimidyl ester (CFSE) cell division assay, as previously described [25]. The stimulation index (SI) was calculated by dividing the percentage of $CFSE^{lo}$ cells in HBsAg-stimulated wells by the percentage in non-stimulated wells. Values below 1% $CFSE^{lo}$ cells in non-stimulated wells were set to 1, to exclude unrealistic high values in SI due to division by values <1. The CD4+ T-cell response was considered positive if the SI was >2 and percent $CFSE^{lo}$ cells in response to HBsAg was at least 5% above the background in non-stimulated wells.

2.6. Statistics

Statistical analysis was performed using Prism 6 for MacOSX. Geometric mean titer antibody (GMT) levels were compared between groups by Mann–Whitney. The proportion of each vaccine group achieving seroprotection (>10 mIU/mL) titer post-immunization was compared by Fisher's exact test. Trends across

Download English Version:

https://daneshyari.com/en/article/10965619

Download Persian Version:

https://daneshyari.com/article/10965619

Daneshyari.com