Vaccine 35 (2017) 1782–1788

Contents lists available at ScienceDirect

Vaccine

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

Safety, tolerability and efficacy of intradermal rabies immunization with DebioJect™

Paul Vescovo [a,*], Nils Rettby [b], Nirinarilala Ramaniraka [a], Julie Liberman [b], Karen Hart [b], Astrid Cachemaille [a], Laurent-Dominique Piveteau [a], Reto Zanoni [c], Pierre-Alexandre Bart [b], Giuseppe Pantaleo [b]

[a] Debiotech SA, Lausanne, Switzerland
[b] Vaccine and Immunotherapy Center, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[c] Institute of Virology and Immunology in cooperation with the Vetsuisse Faculty of the University of Bern, Bern, Switzerland

ARTICLE INFO

Keywords:
Drug delivery
Microneedle
Intradermal injection
Rabies vaccine

ABSTRACT

In a single-center study, 66 healthy volunteers aged between 18 and 50 years were randomized to be immunized against rabies with three different injection routes: intradermal with DebioJect™ (IDJ), standard intradermal with classical needle (IDS), also called Mantoux method, and intramuscular with classical needle (IM). "Vaccin rabique Pasteur®" and saline solution (NaCl 0.9%) were administered at D0, D7 and D28. Antigen doses for both intradermal routes were 1/5 of the dose for IM. Tolerability, safety and induced immunogenicity of IDJ were compared to IDS and IM routes. Pain was evaluated at needle insertion and at product injection for all vaccination visits. Solicited Adverse Event (SolAE) and local reactogenicity symptoms including pain, redness and pruritus were recorded daily following each vaccination visit. Adverse events (AE) were recorded over the whole duration of the study. Humoral immune response was measured by assessing the rabies virus neutralizing antibody (VNA) titers using Rapid Fluorescent Focus Inhibition Test (RFFIT). Results demonstrated that the DebioJect™ is a safe, reliable and efficient device. Significant decreases of pain at needle insertion and at vaccine injection were reported with IDJ compared to IDS and IM. All local reactogenicity symptoms (pain, redness and pruritus) after injection with either vaccine or saline solution, were similar for IDJ and IDS, except that IDJ injection induced more redness 30 min after saline solution.

No systemic SolAE was deemed related to DebioJect™ and classical needles. No AE was deemed related to DebioJect™. No Serious Adverse Event (SAE) was reported during the study.

At the end of the study all participants were considered immunized against rabies and no significant difference in humoral response was observed between the 3 studied routes.

1. Introduction

Most vaccinations today consist in administering a high amount of antigens via the intramuscular (IM) route. Because of the cost of these antigens and sometimes their shortage in availability, their use is limited in many developing countries. Intradermal (ID) administration of several vaccines has been shown to require lower amounts of antigen than IM vaccination, therefore providing a significant economic advantage [1–3]. Four licensed vaccines are currently delivered ID: smallpox (vaccinia), BCG, influenza (INTANZA®/IDflu®, Sanofi Pasteur) and rabies. In particular, in the case of rabies and influenza, several studies have shown that reduced doses (typically 10% or 20% of the standard amount of antigen) delivered ID could induce immune responses similar to those seen with the standard dose through IM route [1,4–6]. For these reasons, ID was confirmed to be a promising method for vaccination [7].

Skin is considered as a desirable vaccination target since dermis and epidermis layers are rich sources of antigen-presenting cells (i.e. Langerhans cells, dermal dendritic cells and dermal macrophages) which are known to participate in vaccine induced immune responses [8,9]. In addition, the dense network of blood capillaries and lymphatic vessels present within the dermis greatly facilitates the trafficking of leukocytes and dendritic cells from skin to the secondary lymphoid organs. However, the Mantoux method is difficult to execute properly in order to ensure a full delivery into the dermis. The technique requires specific training and regular practice of healthcare workers [1,10–12]. Therefore new delivery devices simplifying intradermal injections and rendering them less

* Corresponding author.
E-mail address: p.vescovo@debiotech.com (P. Vescovo).

http://dx.doi.org/10.1016/j.vaccine.2016.09.069
0264-410X/

user-dependent are needed in order to target the skin dermis with its specific immune properties more effectively.

DebioJect™ has been designed for this very purpose. The device is based on a hollow microneedle, whose length is limited to 750 μm to avoid most pain receptors. The microneedle is made of very strong monocrystalline silicon covered with biocompatible silicon dioxide. It has an extremely sharp tip and a lateral delivery aperture located at 500 μm from the base to be minimally invasive and to ensure drug administration into the dermis without risking blocking the injection channel (Fig. 1).

DebioJect™ is designed for easy use by medical staff after a very short training. It is CE marked and can be connected to any standard syringes. An inserter is used to ensure the full penetration of the microneedle into the skin in every circumstance.

ID rabies vaccination is promoted by the World Health Organization (WHO) [13], and has been established for post-exposure prophylaxis in India, the Philippines, Sri Lanka and Thailand [14–18]. Rabies is often considered as a good vaccine candidate for the evaluation of new intradermal device delivery systems [1].

The worldwide burden of human rabies is at an estimated number of 55,000 deaths per year, occurring predominantly in Asia and Africa along with canine rabies [13,19–21]. As no effective treatment is available, vaccination is essential to prevent rabies at both pre- and post-infection stages [16].

Efficient purified rabies vaccines produced in cell-cultures or embryonated eggs were developed more than four decades ago [22]. The "Vaccin rabique Pasteur®" manufactured by Sanofi Pasteur, a purified rabies vaccine cultured on Vero cells, is WHO-approved for pre- and post-exposure prophylaxis by ID and IM routes. WHO recommends a 5-fold antigen dose reduction for the intradermal route compared to the IM route, which is expected to induce a rabies virus neutralizing antibody (VNA) response $\geqslant$ 0.5 IU per mL (International Unit/milliliter), considered as sufficient for protection against rabies [4,22–24].

The objectives of this study were to evaluate DebioJect™ (IDJ) safety, tolerability and induced immunogenicity compared to standard intradermal/Mantoux (IDS) and IM route in the frame of rabies vaccination with "Vaccin rabique Pasteur®".

2. Materials and methods

2.1. Ethics statement

The study was conducted according to Good Clinical Practice, the Declaration of Helsinki, Directive 90/385/CEE and 93/42/CEE, International Standard ISO 14155:2011. The protocol was first approved by the local Institutional Review Board (*Commission cantonale (VD) d'éthique de la recherche sur l'être humain*, reference: 178/12) on July 13th, 2012, and then by Swissmedic, the Swiss Agency for Therapeutic Products (reference: 2012-MD-0030) on June 3, 2013. EUDAMED Identifier: CIV-12-12-009346. ClinicalTrials.gov Identifier: NCT02538185.

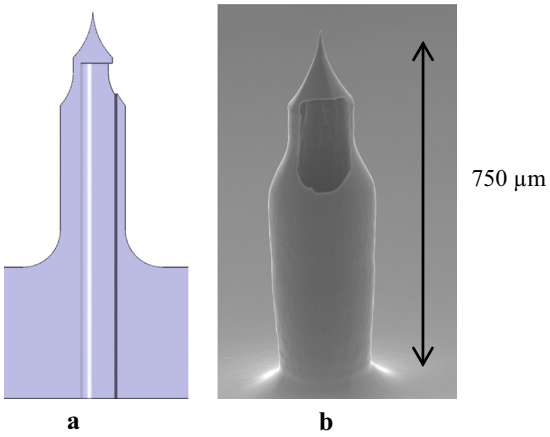

Fig. 1. Schematic cross section (a) and SEM picture (b) of DebioJect™'s hollow microneedle with lateral aperture.

2.2. Study design

The study was planned as a single-center, Phase I, first-in-human pilot study to assess the safety and tolerability of the DebioJect™ device, and the immunogenicity of the rabies vaccine "Vaccin rabique Pasteur®" delivered with the DebioJect™ device by intradermal route. In addition to vaccine, saline solution (NaCl 0.9%; B. Braun) was injected in order to complement safety and tolerability data. Saline solution was not intended to be used as a placebo in the immunogenicity evaluation of the "Vaccin rabique Pasteur®".

The study was conducted at the Vaccine and Immunotherapy Center (VIC), which is a specialized unit of the Service of Immunology and Allergy of the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland, from August 2013 to September 2014. Both volunteers and investigators were blinded regarding the injected substance although they both knew the device used to perform each injection.

2.3. Assessment of IDJ injection completeness

One of the main issues of ID injections based on microneedle is incomplete injection due to leakage [25]. Injection with IDJ was considered to be complete if leakage (non-injected fluid residue present on the skin) represented less than 10% of the volume of the product to be injected. A procedure was implemented to measure the amount of non-injected liquid for each IDJ injection. The procedure consisted of three steps: (1) a blotting paper hermetically sealed in an Eppendorf tube was weighed. (2) The non-injected fluid residue present on the skin was immediately absorbed after the injection with the blotting paper. The blotting paper was replaced in the Eppendorf tube which was then hermetically sealed. (3) Finally the Eppendorf tube containing the wetted blotting paper was weighed again with the amount of non-injected fluid residue corresponding to the weight difference between both measurements.

2.4. Investigational and comparator devices

The investigational device was DebioJect™ developed by Debiotech. The comparator device used for IDS was a 25G needle mounted on a standard syringe. The comparator device used for IM injection was a 22G needle mounted on a standard syringe. The operators involved in the study were selected upon their ability and experience to perform successful Mantoux injection. They were also trained to use DebioJect™.

2.5. Study population

Subjects were recruited in the study only if they were aged between 18 and 50 years and in good general health, confirmed by medical history, physical examination and screening laboratory tests. Female subjects were required to avoid pregnancy through the duration of the study.

The following criteria caused the exclusion of the study group: an oral body temperature $\geqslant$ 37.5 °C; any history or evidence of rabies vaccination or rabies contact, autoimmune disease, any possible immunodeficiency state, including HIV-1 infection, and of chronic hepatitis; any injection of immunoglobulin or blood