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Immunogenicity and safety of the new intradermal influenza vaccine in adults and elderly: A randomized phase 1/2 clinical trial

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ABSTRACT

Background: Recent clinical evidence indicates that an intradermal (ID) delivery of vaccines confers superior immunogenicity as compared to a standard intramusclular or subcutaneous (SC) delivery.
Methods: In this exploratory study, 600 healthy adults were randomized to 6 study groups with subgroups of young adults (20–64 years old) and older adults (65 years and older). The subjects were either injected by a novel ID injection system with a single dose of 6, 9, or 15 μg HA or two doses (21 days apart) of 15 μg HA per strain or injected by an SC injection method with a single or two doses (21 days apart) of 15 μg HA per strain. Immunogenicity was assessed using hemagglutination inhibition (HAI) titer and microneutralization titer on Days 0, 10, 21, and 42. Solicited and unsolicited adverse events were recorded for 7 and 21 days post-vaccination, respectively.
Results: In both young adults and older adults groups, the geometric titer (GMT) ratios of HAI in the ID 15 μg HA group were higher than those in the SC 15 μg HA group on both Day 10 and Day 21, while those in the ID 6 and ID 9 μg HA groups were comparable with those in the SC 15 μg HA group. The kinetics of GMTs of HAI suggested that the ID vaccine has the potential to induce the prompt immune response, which is rather hampered in older adults as seen in the SC vaccine groups. The injection-site AEs were generally mild and transient, and did not occur in a dose or dosage-dependent manner.
Conclusions: The results of this study clearly suggest that the immunologic profile of the ID vaccine is better than that of the SC vaccine, while the safety profile of the ID vaccine is similar to that of the SC vaccine. In this exploratory study with almost 100 subjects per each group, single or two-dose administration of the ID vaccine containing 15 μg HA was suggested to be an appropriate regimen in order to prevent influenza and to reduce the associated disease burden.
Trial registration: JAPIC Clinical Trials Information (JapicCTI-132096).

1. Introduction

Influenza remains a significant cause of morbidity and mortality worldwide, resulting in a major public health concern. Despite preventive efforts, seasonal influenza virus infections are estimated to cause 3–5 million cases of severe illness and up to 250,000–500,000 deaths every year worldwide [1]. It is still difficult to control influenza outbreaks, epidemics, and/or pandemics, because of the nature of influenza viruses, such as the antigenic drift occurring every season, changes of host/tissue tropism from natural reservoirs, i.e. transmission from swine and/or birds to humans, and the high transmissibility due to the short incubation period to reproduce infectious viruses [2].

In order to prevent from influenza virus infection and to reduce the burden of influenza-associated diseases, vaccination strategies have been implemented and cover children 6 months and older, adolescents, young adults, and the elderly [1]. Standard influenza vaccines currently used contain the tri- or quadri-valent hemagglutinin (HA) antigen derived from inactivated influenza virus and are administered either intramuscularly (IM) or subcutaneously (SC), the latter being used exclusively in Japan. The number of doses and dosage of vaccines vary depending on the age, underlying diseases, and conditions of the vaccinee [1]. In Japan, the

Abbreviations: ID, intradermal; SC, subcutaneous; HA, hemagglutinin; HAI, hemagglutination inhibition; NT, microneutralization; GMT, geometrical mean titer; GMTR, GMT ratio; SCR, seroconversion ratio; SPR, seroprotection ratio; AE, adverse event; CHMP, The Committee for Medicinal Products for Human Use.

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recommended number of doses for the seasonal influenza vaccine is one or two doses for 13 years and older. Among target populations, the elderly, in general, need to securely acquire the protective immunity because they are more vulnerable to death and hospitalization due to influenza and at higher risk of deterioration from underlying diseases upon influenza infection as compared with healthy young adults [1]. Standard influenza vaccines have, however, a lower immunogenicity in the elderly than in young adults [3].

In order to improve influenza vaccine efficacy, various approaches have been made over decades, including the change of administration route, i.e., intradermal, transdermal, or intranasal route, and the change of formulation, i.e., addition of new adjuvants, an increase of the antigen dosage, or the usage of different antigen types. Among these, it has been clinically demonstrated that influenza vaccines delivered by several different types of intradermal (ID) injection and those formulated with a novel adjuvant have unique profiles in immunogenicity and usability superior to the standard ones and some of such products have been introduced into the market since the late 2000s [4–6].

Accumulating evidence has indicated that the immunogenicity of vaccines is modulated depending on the route of administration. ID vaccination has the advantages of immunogenicity, safety, tolerability, and acceptability over IM or SC vaccination [4,7]. In fact, as a dose-sparing, the World Health Organization (WHO) recommend the ID administration of a reduced dosage of the rabies vaccine originally used for the IM injection with an expectation to improve vaccination coverage for post-exposure prophylaxis in low-income countries [8]. However, thus far, the ID delivery has been used as a route for limited licensed vaccines, including Bacillus Calmette–Guérin (BCG) for tuberculosis and a new type of influenza HA vaccine with an injection device specifically for the ID delivery [4,7].

The accuracy and the consistency of an ID administration by the Mantoux technique with a standard syringe and needle mostly depend on the performance of the practitioner. In order to offer a simple, accurate, consistent, and safe ID administration, several different devices specifically for the ID injection have been developed [4,9–12].

In this exploratory dose-finding study, we investigated the immunogenicity and safety of two different numbers of doses (single and two-dose) and three different dosages (6, 9, and 15 μg HA per dose) of the influenza vaccine with the novel ID injection system (Immucise®, Terumo Co., Tokyo, Japan) by comparing it with the standard SC vaccine (15 μg HA per dose). As a result, we have decided the number of doses and dosage of the novel ID vaccine appropriate for clinical use and will further examine its efficacy and safety profile in the confirmatory studies and its application for infants and adolescents.

2. Materials and methods

2.1. Study design and objectives

This phase 1/2, randomized, active control, parallel-group study was conducted at four centers in Japan in 2013. The objective of this study was an evaluation of the number of doses and dosage of the novel ID vaccine by comparing it with the standard SC injection type seasonal influenza vaccine in healthy adults aged 20 years old and older.

The randomization lists were prepared by using a permuted block randomization method. Six hundred subjects were randomized at an equal ratio to the four different groups for the ID vaccine (single-dose of 6, 9, or 15 μg HA and two-dose of 15 μg HA) and the two different groups for the SC vaccine (single-dose or two-dose of 15 μg HA). The ratio of 20- to 64-year-old subjects (Young Adult subgroup) to 65 years and older subjects (Older Adult subgroup) was 1:1 in each vaccine group. The ID vaccine groups of single-dose 6, 9, and 15 μg HA were double-blinded.

On Day 0, blood was taken and then the first vaccination was conducted in all groups. On Day 10 (7–13 days after the first vaccination), blood was taken in the single-dose groups. On Day 21 (14–28 days after the first vaccination), blood was taken in all groups and then the second vaccination was conducted in the two-dose groups. On Day 42 (14–28 days after the second vaccination), blood was taken in the two-dose groups. The appearance of shock and anaphylaxis was checked in all groups up to 30 min after each vaccination.

This study was approved by the institutional review boards of each study center. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all subjects before enrollment.

2.2. Subjects

Healthy Japanese adults aged 20 years and older were eligible to participate in this study. The main exclusion criteria included: any history of seasonal influenza in the past six months, any history of seasonal influenza vaccination in the past six months, an axillary temperature $\geq$37.5 °C, severe acute illness, any history of intolerance or anaphylaxis to the study vaccine components or the ID injection system, and past medical history of diseases which were described as severe AEs (e.g. acute disseminated encephalomyelitis and thrombocytopenia purpura).

2.3. Vaccines

All vaccines contain inactivated, trivalent, split-virion influenza hemagglutinin (HA) derived from A/California/7/2009/(H1N1)pdm09, A/Victoria/361/2011(H3N2), and B/Wisconsin/1/2010 vaccine strains recommended by the Ministry of Health, Labor, and Welfare in Japan for the 2012/13 season. All vaccines were manufactured by using embryonated eggs at Kitasato Daiichi Sankyo Vaccine Co., Ltd (Saitama, Japan). The ID vaccine was administrated with a dose of 0.1 mL containing 6, 9, or 15 μg of HA per strain per dose using the ID injection system (Immucise®, Terumo Co., Tokyo, Japan). The ID injection system consists of a needle assembly with a single 33-gauge needle and a syringe. As a control, the licensed influenza vaccine was administered as an SC dose of 0.5 mL containing 15 μg of HA per strain per dose. The ID vaccine was administrated in the deltoid area of the upper arm, while the SC vaccine was administrated into an extensor side of the upper arm.

2.4. Immunogenicity assessment

Immunogenicity was assessed using hemagglutination inhibition (HAI) titers and microneutralization (NT) titers in a blinded manner. HAI titers were measured by using turkey red blood cells, while NT titers were measured by using each vaccine strain of influenza viruses. Both antibody titers were measured at VisMederi srl (Siena, Italy). HAI titer was defined as the reciprocal of the highest dilution at which hemagglutin (HA) activity was totally inhibited. The titer of each sample was calculated as the average of its duplicate. NT titers were determined as the reciprocal of the serum dilution at which at least 50% inhibition of cytopathogenic effect was achieved, and then calculated according to the Spearman-Kärber formula. Based on the criteria for seasonal influenza vaccine of The Committee for Medicinal Products for Human Use (CHMP), immunogenicity was assessed based on the geometric mean titer (GMT) of HAI, the seroprotection