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Dose sparing intradermal trivalent influenza (2010/2011) vaccination overcomes reduced immunogenicity of the 2009 H1N1 strain

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ABSTRACT

Background: We hypothesized that low dose intradermal vaccination of the trivalent influenza vaccine (TIV) delivered by the MicronJet600™ (NanoPass Technologies, Israel) would be non-inferior to the full dose intramuscular and mid dose Intanza® vaccination in the elderly and the chronically ill adults.
Methods: We performed a prospective randomized trial on elderly and chronically ill adults. Subjects were randomly assigned into 4 groups. Groups ID3 and ID9 received reduced dose ID TIV (3 μg and 9 μg of hemagglutinin (HA) per strain respectively) delivered by MicronJet600™ (NanoPass Technologies, Israel). Group INT9 received reduced dose ID TIV (9 μg) delivered by Becton Dickinson's Soluvia™ device (Intanza®9, Sanofi-Pasteur, France). Control group IM15 received a full dose IM TIV (15 μg). We measured antibody titers by hemagglutination inhibition (HAI) and microneutralization (MN) assays at baseline and day 21.
Results: Baseline characteristics for all groups were similar (group and sample sizes: ID3 = 63; ID9 = 68; INT9 = 65; and IM15 = 66). At day 21 post vaccination, the GMT ratio and the seroconversion rates difference for all three strains of the ID vaccine groups were non-inferior to the IM vaccine group. The seroconversion rate, seroprotection rate, and the GMT of the H1N1 strains by HAI and MN assays were significantly higher in the ID groups compared with the full dose IM vaccine group. The seroconversion rates of the H3N2 strain by HAI assay were also significantly higher in the ID groups when compared with the full dose IM group. Direct comparison among the three ID groups showed no significant differences. No serious adverse events related to vaccination were reported.
Conclusion: Dose-sparing ID TIV can overcome reduced immunogenicity of the H1N1 strain, and according to some measures, for the H3N2 strain. At risk subjects indicated for the TIV should be considered for intradermal immunization to compensate for reduced immunogenicity.

1. Introduction

Influenza presents a substantial public health threat and a significant burden on health authorities worldwide, even in non-pandemic years [1]. Seasonal influenza is estimated to infect between 5% and 20% of the population annually, resulting in over 200,000 hospitalizations and about 36,000 deaths in the US alone [2]. Influenza infection can cause life-threatening pneumonia and extrapulmonary complications. In addition, it can lead to substantial "non-infectious" morbidity and mortality [3]. Influenza vaccination has recently been shown [4,5] to prevent both respiratory and vascular complications in the elderly and patients with chronic illness. Furthermore, neuraminidase inhibitors, the only antiviral licensed for clinical use were not very effective in the clearance of virus in the late presenters [6]. Prevention via vaccination is considered the most important means to combat against influenza [7].

Elderly subjects present a particular challenge for immunization against seasonal and pandemic influenza due to the unfortunate combination of the reduced ability to mount protective response to vaccine due to immunosenescence [8] on one hand, and their increased vulnerability to morbidity and mortality due to influenza virus and its complications [9] on the other hand. About 86% of the all-cause mortality attributed to seasonal influenza occurs in the elderly [10]. The need to improve the immunization of the elderly is well established [11].

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Recent report suggested possibly reduced effectiveness of the 2009 H1N1 component of live attenuated influenza vaccine (LAIV) for the 2010–2011 influenza season [12] corresponding with an increased number of influenza cases among military recruits who received the LAIV. Low immunogenicity of the intramuscular non-adjuvanted 2009 H1N1 monovalent vaccine was also reported [13]. Dose-sparing intradermal (ID) vaccination with different delivery devices have demonstrated non-inferior immunogenicity in seasonal influenza vaccination compared with conventional intramuscular vaccination before the pandemic H1N1 2009 [14–17]. However, this strategy has not been tested for the trivalent influenza vaccine (TIV) after this pandemic. We therefore performed a prospective randomized controlled study to compare the safety and immunogenicity between conventional full dose intramuscular (IM) and reduced dose ID immunization delivered by two different devices.

The two intradermal injection devices used in this study include the BD Soluvia™ microinjection and the MicronJet600™ systems. The Intanza® (Sanofi-Pasteur) with the BD Soluvia™ microinjection system consists of a prefilled trivalent influenza vaccine, with a single 1.5 mm needle penetrating perpendicularly to the skin [14–16]. On the other hand, the MicronJet600™ system consists of an array of three microneedles each 0.6 mm in length, puncturing obliquely into the skin. The BD Soluvia™ is currently the only prefilled intradermal device licensed for influenza vaccine.

2. Materials and methods

A prospective randomized, open-label, single-center trial was conducted at Queen Mary Hospital from 25 November 2010 to 24 February 2011. We compared the safety and immunogenicity of a single low-dose (3 μg and 9 μg HA, respectively) ID TIV administration with a single full-dose (15 μg) IM administration. The vaccine used was Intanza® (Sanofi-Pasteur) for the ID groups and Fluzone® (Sanofi-Pasteur) for the IM group. The TIV used was an inactivated, non-adjuvanted vaccine formulated to contain 15 μg of HA of influenza A/California/07/2009 (H1N1)-like virus, influenza A/Perth/16/2009 (H3N2)-like virus and influenza B/Brisbane/60/2008-like virus. We recruited elderly and chronically ill adults aged ≥21 years who satisfied the WHO recommendation for annual vaccination against influenza. The study was approved by the Institutional Review Board of the Hospital Authority of Hong Kong and is registered with the ClinicalTrials.gov, number NCT01304563.

Subjects were assigned by a randomization list. Groups ID3 and ID9 received a reduced dose ID TIV (3 μg and 9 μg of HA per strain, respectively) with MicronJet600™. Group INT9 received a reduced dose ID TIV (9 μg) with BD Soluvia™ device (Intanza®9). Group IM15 received the full-dose standard IM TIV (15 μg). All patients recruited gave written informed consent. Patients with clinically significant immune-related diseases, recent comorbidities and history of allergy to the components of the vaccine were excluded.

Safety was evaluated by asking the subjects to remain in the clinic premise for 30 min for observation post immunization. An immediate adverse event checklist was filled before discharge, covering the period for severe anaphylactic reaction. A diary was given to the subjects to document symptoms of local and systemic adverse events presented within the first 7 days post-vaccination. Systemic symptoms included fever (body temperature ≥ 37.5 °C), headache, malaise, myalgia and arthralgia, and local symptoms included redness, swelling, induration, pain and ecchymosis were documented as solicited events. The diaries were collected upon follow-up on day 21-post vaccination.

Antibody titers were measured using hemagglutination-inhibition (HAI) and microneutralization (MN) assays according to standard methods as described previously, at baseline and 21 days after vaccination [18,19].

Specific study personnel who did not take part in the subsequent assessment of safety or immunogenicity performed all vaccinations. The primary outcome measure is the immunogenicity by seroconversion rate, defined as the percentage of subjects with an HAI antibody titer < 10 at baseline and a post-vaccination titer of ≥40 or a titer > 10 at baseline and at least a four-fold increase in titer post-vaccination on day 21. Secondary outcome measures included geometric mean titer (GMT) fold increases in antibody titer and adverse events of 30 min post vaccination. Seroprotection rate was also reported as defined by percentage of subjects with HAI and MN antibody titer ≥ 40 on day 21.

Based on previous study of the seroconversion rate of 82% for the intradermal seasonal influenza vaccination with a dosage of 3 μg HA per strain and 70% seroconversion rate for the regular 15 μg HA per strain intramuscular vaccination, we calculated that a total sample of 40 subjects per group would be needed to demonstrate non-inferiority [14], based on a two-sided test, Type 1 error rate of 5%, 80% power and a non-inferiority tolerance margin of 1.5. The protocol proposed recruiting 60 subjects per group, with a threshold of at least 50 to allow for 25% drop out rate. Demographic parameters and adverse reactions were compared by Fisher's exact test for categorical variables and by Kruskal–Wallis test for continuous variables. Student's *t*-test was used to compare the GMT and GMT folds increases between each of the study and control groups. Non-inferiority of each of the ID vaccine group against the intramuscular vaccine group was assessed by the day 21 post-vaccination GMT ratio and the seroconversion rates for all three strains [20,21]. Non-inferiority was defined as the upper limit of the 2-sided 95% CI of the GMT ratio (intramuscular vaccine/intradermal vaccine) not exceeding 1.5 and the upper limit of the 2-sided 95% CI for the difference in seroconversion rates (intramuscular vaccine minus intradermal vaccine) not exceeding 10% for all three strains [20,21]. Fisher's exact test and logistic regressions were conducted to compare seroconversion and seroprotection rates among the 4 groups. Correlation between post-vaccination swelling and subsequent GMT value and fold increase, seroconversion/seroprotection rate on day 21 was analyzed by Spearman rho. SPSS 18.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical computation. P value < 0.05 was considered to represent significant difference.

3. Results

3.1. Subjects

A total of 282 subjects were enrolled of which 262 completed the study. Sixty-three subjects (ID3) received a reduced dose ID TIV (3 μg of HA per strain) with MicronJet600™, 68 subjects (ID9) received a reduced dose ID TIV (9 μg) with MicronJet600™, 65 subjects (INT9) received a reduced dose ID TIV (9 μg) with BD's Soluvia™ device (Intanza®9), and 66 subjects (IM15) received the full-dose standard IM TIV (15 μg). Twenty subjects were lost to follow-up. Dropout rates were similar among the groups ($p = 0.535$) and related to compliance, rather than specific adverse events. The four groups did not differ in terms of baseline demographics including age, gender, background diseases and vaccination history (Table 1). Majority of the patients have had hypertension only as past medical history. None of the patients enrolled were on long-term immunosuppressants. Forty-three patients (16.4%) received IM monovalent H1N1 2009 vaccine in the previous year. This vaccination history was not significantly different amongst the four groups.