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Comparative immunogenicity of trivalent influenza vaccine administered by intradermal or intramuscular route in healthy adults

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Abstract

The present study was undertaken with controls using equal doses ID and IM plus the standard full dose IM to assess the role of route of vaccine in immunogenicity of inactivated influenza vaccine. The study was a prospective, randomized, active-controlled, open label clinical trial conducted in healthy young adult outpatients to compare the effect of route (IM versus ID) on antibody responses to influenza vaccine. Volunteers received 3, 6 or 9 μg of vaccine by ID or IM route; 15 μg IM was also studied. Low doses of vaccine given by either route were almost as immunogenic as the standard 15 μg IM dose of influenza vaccine. ID route was not superior to IM vaccine at inducing antibodies. ID vaccine induced significantly more local inflammatory response than IM vaccine.

Keywords: Influenza; Vaccine; Route

1. Introduction

Routine yearly administration of influenza vaccine to adults is a long-standing recommendation, and in 2006 the recommendation was further extended to children 6 months to 5 years of age. Moreover, inactivated trivalent influenza vaccine (TIV) may be administered to anyone over 6 months of age wishing to reduce the risk of contracting influenza. Influenza vaccines have repeatedly been shown to be effective at reducing influenza related morbidity and mortality [3–6]. The extension of the influenza vaccine recommendations to include children and household contacts of high-risk persons has increased the number of influenza doses needed to be produced [7]. Currently, 180 million persons are recommended to receive vaccine. In recent years there has been a shortage of vaccine, particularly in the fall months of the year when most providers and patients seek influenza vaccine. We and others have conducted trials on lower doses of vaccine and other administration routes to try and stretch vaccine supply [1,2]. One possible method is the intradermal (ID) administration of partial doses of influenza vaccine.

Recently, we and others demonstrated that in healthy adults lower doses (3 or 6 μg) of TIV administered ID produced immune responses equivalent to a standard dose of TIV (15 g per HA) administered IM [1,2]. While local reactions were more common in the group receiving TIV by ID injection, the systemic safety profile was similar in the group receiving ID injections as compared to IM. However, in these studies, rigorous controls (i.e. low dose IM) were not included in the design. The present study was undertaken with controls using equal doses ID and IM plus the standard

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full dose IM to assess the role of route of vaccine in immunogenicity.

2. Materials and methods

2.1. Trial design

The goals of the study were to compare the immunogenicity and safety of injection of TIV across different dose levels (3, 6, 9, and 15 μg/antigen/dose) and different routes of administration (IM versus ID). The study was a single-center, prospective, randomized, active-controlled, open label clinical trial. Approximately 31 subjects per group (217 in total) were to be enrolled to each of the following groups determined by dose and route of administration:

Dose (μg)	Vaccine, route	
	TIV, IM (mL)	TIV, ID
15	0.5	N/A
9	0.3	0.1 mL × 3
6	0.2	0.1 mL × 2
3	0.1	0.1 mL × 1

Two sera samples were taken, one on Day 0 before vaccination (baseline) and one on approximately Day 28 post-vaccination, to assess immunogenicity.

2.2. Subjects

Healthy adults between the ages of 18 and 49 were recruited into the study after providing informed consent approved by the Saint Louis University Institutional Review Board. Subjects were excluded if they were breastfeeding or pregnant, had a history of receiving influenza vaccine in any of the three previous years, were allergic to eggs or other components in the vaccine, had a history of Guillain–Barré syndrome or immunosuppression or any condition that in the opinion of the investigator would interfere with the evaluation of antibody responses to the vaccine. Female subjects were tested by urine pregnancy test and had to be negative prior to vaccination. The subjects included 147 (68%) women and 70 (32%) men; 29 (13%) were black, 182 (84%) were white, and the remainder other. Details by group are given in Appendix A.

2.3. Vaccine and vaccine administration

Trivalent inactivated influenza vaccine (Fluzone®, Sanofi-pasteur, Swiftwater, PA) was used in the study. The Mantoux technique was used to administer .1 mL of vaccine into the non-dominant upper arm (deltoid region). One Mantoux injection was used for 3 μg; two Mantoux injections were used for 6 μg injection; and three Mantoux injections were used for 9 μg injections. All injections were given in the same arm and were separated by 5 cm distance. Intramuscular TIV was given in the non-dominant arm; .1, .2, .3 mL or the standard .5 mL volume was administered corresponding to 3, 6, 9 or 15 μg of each HA antigen in the vaccine.

2.4. Reactogenicity

The safety endpoints assessed the frequency and severity of solicited local and systemic symptoms collected at 30 min post-vaccination, during the 7-day period following vaccination (reactogenicity), all unsolicited adverse events (AEs) through Day 28, and serious adverse events (SAEs) during the length of the study. The number and proportions of subjects in each group experiencing any injection site or systemic symptoms, and the proportions of subjects who experience moderate-to-severe symptoms were determined for each vaccine dose and route.

After vaccination, subjects were provided with a memory aid (diary card), a digital thermometer and a flexible centimeter ruler, and were instructed how to record their reactogenicity responses on the day of vaccination and daily for the 7 days after vaccination. They recorded their maximum daily oral temperature (in degrees Fahrenheit), maximum daily erythema and swelling (in centimeters), maximum severity grade of all other solicited injection site and systemic reactions, any other adverse events, and any new medications or changes in medications. Volunteers who received more than one Mantoux injection were instructed to record the measurements at all of the sites. The maximum reaction was used for safety analysis.

Subjects were contacted by telephone on Days 8–12 after vaccination to collect memory aid information and to assess AEs and SAEs.

Solicited injection site reactions and systemic reactions were defined and graded according to Tables 1 and 2.

2.5. Immune responses to vaccine

Immunogenicity was evaluated using the hemagglutination-inhibition assay (HAI) on serum samples collected prior to vaccination and at day 28 (±3 days) post-vaccination. The assessment of the immune response to the vaccine included the following: (1) the geometric mean titer (GMT) of serum HAI antibody measured against each of the three vaccine antigens; (2) the proportion of subjects in each group who achieved a serum HAI antibody titer of at least 1:32 for each of the three vaccine antigens after vaccination; and (3) the proportion of subjects achieving at least a four-fold increase in serum HAI antibody titer between pre-immunization and post-immunization serum samples. Paired serum samples were tested by HAI against all three strains of virus (influenza A/H1N1/, influenza A/H3N2, and influenza B) using turkey red blood cells [8]. The antigens used in the assay were comparable to the strains of virus in the TIV.