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A phase 1, open-label, randomized study to compare the immunogenicity and safety of different administration routes and doses of virosomal influenza vaccine in elderly

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ABSTRACT

Background: Influenza remains a significant problem in elderly despite widespread vaccination coverage. This randomized, phase-I study in elderly compared different strategies of improving vaccine immunogenicity.

Methods: A total of 370 healthy participants (⩾65 years) were randomized equally 1:1:1:1:1:1 to six influenza vaccine treatments (approximately 60–63 participants per treatment arm) at day 1 that consisted of three investigational virosomal vaccine formulations at doses of 7.5, 15, and 45 μg HA antigen/strain administered intradermally (ID) by MicronJet600™ microneedle device (NanoPass Technologies) or intramuscularly (IM), and three comparator registered seasonal vaccines; Inflexal V™ (Janssen) and MF59 adjuvanted Fluad™ (Novartis) administered IM and Intanza™ (Sanofi Pasteur) administered ID via Soluvia™ prefilled microinjection system (BD). Serological evaluations were performed at days 22 and 90 and safety followed-up for 6 months.

Results: Intradermal delivery of virosomal vaccine using MicronJet600™ resulted in significantly higher immunogenicity than the equivalent dose of virosomal Inflexal V™ administered intramuscularly across most of the parameters and strains, as well as in some of the readouts and strains as compared with the 45 μg dose of virosomal vaccine formulation. Of 370 participants, 300 (81.1%) reported ⩾1 adverse event (AE); more participants reported solicited local AEs (72.2%) than solicited systemic AEs (12.2%).

Conclusions: Intradermal delivery significantly improved influenza vaccine immunogenicity compared with intramuscular delivery. Triple dose (45 μg) virosomal vaccine did not demonstrate any benefit on vaccine's immunogenicity over 15 μg commercial presentation. All treatments were generally safe and well-tolerated.

1. Introduction

Influenza results in about 3–5 million cases of severe illness and 250,000–500,000 deaths every year, globally [1]. Over 90% of these deaths and ~50% of hospitalizations occur among individuals' ⩾65 years of age [2,3]. Regardless of the progressive increase in influenza vaccine coverage, the rates of hospitalization and deaths due to seasonal influenza in elderly individuals have continued to increase substantially in the past decades [4–6]. The elderly patients present a particular immunization challenge for influenza due to the unfortunate combination of reduced immunity (immunosenescence) and an increased vulnerability to morbidity and mortality [7,8].

Various strategies have been developed to improve the immunogenicity of influenza vaccine in this population, which includes adjuvantation, increasing antigen dose, and more recently, delivering the vaccines intradermally [6,9–16]. Modern adjuvant and carrier systems (e.g., virosomes) can increase the immunogenicity without compromising vaccine safety and tolerability, especially in populations with immunosenescence [17]. Intradermal (ID) administration of vaccines has demonstrated

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improved immunogenicity compared with intramuscular (IM) route of administration in older adults [14,18]. Attempts to increase immunogenicity by increasing the antigen content demonstrated superior relative efficacy over standard dose [6,14,19,20].

Vaccination of the elderly presents a number of challenges including suboptimal immunogenicity and hence decreased vaccine efficacy [21]. There is an unmet medical need to evaluate whether the immune response after vaccination can be further improved through alternative vaccine delivery such as intradermal delivery, a higher intramuscular dose administration or through the use of adjuvants [22]. Moreover, to counteract the known phenomenon of immunosenescence in elderly, commonly used approach is to use a high IM dose or intradermal administration of a standard or lower vaccine dose [23]. In addition, the device used for intradermal administration may have an influence on the antigen delivery to the intradermal layer of the skin, and consequently the level of the immune response and should be taken into consideration.

The aim of this exploratory study was to perform immunogenicity and safety assessments of different administration routes and doses of influenza vaccine, across investigational virosomal vaccine formulations and registered vaccine comparators. We used the European Committee for Medicinal Products for Human Use (CHMP/EMA) criteria for re-licensure of influenza vaccine as a basis of analysis and comparison. This study was not designed to make statistical comparisons of equivalency or non-inferiority across different vaccines, rather, sample size was planned to meet the minimal requirements of influenza vaccine re-licensure (e.g. 50 per treatment arm). Several pairwise comparisons of immune responses of vaccines delivered ID versus IM, standard versus high dose formulation, and investigational (e.g. adjuvanted) versus comparator (same dose, IM) were statistically evaluated.

2. Materials and methods

2.1. Study population

Medically stable, healthy participants ($\geqslant$65 years) who were vaccinated against influenza in season 2011–2012 were enrolled in the study. Exclusion criteria included previous vaccination with an influenza vaccine for season 2012–2013, previous history of a serious adverse events [SAE] or allergic reaction to influenza vaccine, acute exacerbation of bronchopulmonary infection or other acute disease, acute febrile illness (temperature $\geqslant$38 °C), and participation in another clinical trial.

2.2. Study design

This randomized, open-label, phase I study was conducted in 6 centers in Belgium and Germany between November 2012 and July 2013. Elderly participants received influenza vaccine with strain composition for season 2012–2013 either via IM or ID administration at baseline (day 1). Serological evaluations were performed at days 22 (within ±3 days) and 90 (±5 days), and safety was followed-up for 6 months (±7 days).

In total, 370 Participants were stratified by gender and study site and randomized approximately equally 1:1:1:1:1:1 by a web-based procedure to 1 of 6 vaccinations that consisted of three investigational virosomal influenza vaccine formulations and three comparator registered seasonal vaccines. Enrolled number of participants in each of the 6 treatment arms ranged from 60 to 63 (Table 1).

The study protocol and amendments were reviewed by an independent Ethics Committee or Institutional Review Board, as appropriate, for each site. All studies were conducted in compliance with Declaration of Helsinki consistent with Good Clinical Practices and applicable regulatory requirements. Written informed consent was obtained from all participants before enrollment.

2.3. Vaccines

All vaccines used in this study contained as active ingredient the following 3 influenza serotypes recommended for vaccine use during 2012–2013 season: A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), and B/Wisconsin/1/2010 like viruses.

Modern adjuvant and carrier systems (e.g., virosomes) can increase immunogenicity [24–26] especially in populations with reduced responsiveness to active immunization [21]. Virosomes (vir) were produced by inserting purified antigens from inactivated influenza viruses propagated in fertilized hens' eggs into a bilayer of phospholipid vesicles (approximately 150 nm in diameter) composed of predominantly of phosphatidylcholine in phosphate buffered saline [27].

Investigated virosomal influenza vaccines (surface antigen, inactivated, virosome) were formulated as virosomes containing influenza antigens from strains for 2012–2013. The formulations were presented as suspension for injection in a prefilled syringe (type I glass) fitted with a needle size of 25G and 5/8″ (0.5 mm × 16 mm) for intramuscular (IM) injection and with MicronJet600™ microneedle (MJ) device for intradermal (ID) injection, (a disposable 3-prong 0.6 mm hollow microneedle device that attaches to any standard luer lock or luer tip syringe [NanoPass

Table 1
Study influenza vaccines, type, route of administration, dose and volume.

Vaccine identification	Vaccine type/brand	Route of administration	Dose (μgHA/strain)	Volume (mL)
Investigational				
Inflexal-ID-MJ-7.5vir	Surface purified antigen, inactivated virosome[a]	ID (MJ600)	7.5 μg	0.085
Inflexal-ID-MJ-15vir	Surface purified antigen, inactivated, virosome[a]	ID (MJ600)	15 μg	0.17
Inflexal-IM-NS-45vir	Surface purified antigen, inactivated, virosome[a]	IM	45 μg	0.5
Comparators				
Inflexal-IM-NS-15vir	Inflexal V™ surface purified antigen, inactivated, virosome	IM	15 μg	0.5
Fluad-IM-NS-15adj	Fluad™ adjuvanted, surface antigen, inactivated	IM	15 μg	0.5
Intanza-ID-SO-15	Intanza™ split-viron, inactivated	ID	15 μg	0.1

Notes: study vaccines were identified by a naming convention: name-route of administration-delivery device-dose-adjuvant.
ID = intradermal, IM-intramuscular, MJ, MJ600 = MicronJet600™ microneedle (NanoPass Technologies), NS = needle-syringe, SO = Soluvia™ minineedle (Becton Dickinson), vir = virosomal, adj = adjuvant, HA = Hemagglutinin.
Inflexal V™ (Crucell Switzerland) is seasonal Virosomal Influenza Vaccine (surface antigen, inactivated).
Fluad™ (Novartis Vaccines and Diagnostics SRL, Italy) adjuvanted with MF-59™ (oil-in-water emulsion of squalene oil) is a seasonal adjuvanted, subunit (HA and neuraminidase) influenza vaccine.
Intanza™ (Sanofi Pasteur, Lyon, France) is an inactivated, split-virion influenza vaccine.
[a] The purified antigens from inactivated influenza viruses (mainly HA antigens) are presented on a phospholipid bilayer vesicle called a virosome.