Vaccine 29 (2011) 9544–9550

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Safety, tolerability, and immunogenicity of inactivated trivalent seasonal influenza vaccine administered with a needle-free disposable-syringe jet injector

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ARTICLE INFO

Article history:
Received 22 June 2011
Received in revised form 22 August 2011
Accepted 25 September 2011
Available online 8 October 2011

Keywords:
Jet injection
Influenza
Vaccine
Safety
Immunogenicity
LectraJet® M3 RA

ABSTRACT

Background: Jet injectors (JIs) avoid safety drawbacks of needle–syringe (N–S) while generating similar immune responses. A new generation of disposable-syringe jet injectors (DSJIs) overcomes the cross-contamination risk of multi-use-nozzle devices used in 20th-century campaigns. In the first study in humans, the newly-US-licensed LectraJet® model M3 RA DSJI was compared to N–S.
Methods: Sixty healthy adults received one 0.5 mL intramuscular dose of the 2009–2010 seasonal, trivalent, inactivated influenza vaccine (TIV) in randomized, double-masked fashion by either DSJI ($n = 30$) or N–S ($n = 30$). Adverse reactions were monitored for 90 days after injection, and serologic responses assayed by hemagglutination inhibition (HI) at days 28 and 90.
Results: There were no *related* serious adverse events (SAEs), nor differing rates of unsolicited AEs between DSJI and N–S. Solicited erythema and induration occurred more often after DSJI, but were transient and well-tolerated; a trend was noted for fewer systemic reactions by DSJI. Pre-vaccination HI geometric mean titers (GMT) increased by 28 days for H1N1, H3N2, and B antigens by 13-, 14-, and 8-fold via DSJI, and by 7-, 10-, and 7-fold for N–S, respectively. No trending differences in GMT, seroconversion, or seroprotection were noted; sample sizes precluded non-inferiority assessment.
Conclusions: DSJI delivery of TIV is well-tolerated and immunogenic.

1. Background

Needle-free vaccine delivery has the potential to lead to significant advances in immunization, including improved safety for the vaccinator and vaccinee, better compliance with immunization schedules, decreased fear of injection and needles, easier and speedier vaccine delivery, and reduced cost [1]. For these reasons, needle-free vaccine delivery has been supported by the World Health Organization [2], the Global Alliance for Vaccines and Immunization [3], and the Centers for Disease Control and Prevention [4].

Needle-free jet injectors (JI) are devices that use pressure to deliver the drug or vaccine into different parts of the human body, such as skin, muscle, or fat. They have been used since the late 1940s to deliver millions of vaccine doses [5]; the first devices were multiple-use nozzle jet injectors "MUNJIs" whereby the vaccine was delivered through the same fluid stream and nozzle for multiple patients. After an outbreak of hepatitis B virus infection in a weight reduction clinic in 1985 [6], and upon a growing body of evidence for possible cross-contamination, such devices are no longer used in public health [7]. More recent development efforts have resulted in disposable syringe jet injectors, "DSJI", which provide a completely non-reusable fluid pathway so that splash back of blood cannot occur [7].

We report a first human safety and immunogenicity study of trivalent inactivated influenza vaccine (TIV) administered by the LectraJet® M3 RA DSJI, cleared for sale and use by the U.S. Food and Drug Administration in 2009 (FDA 510(k) #K090959) based on substantial equivalence to legally marketed predicate devices [8].

Abbreviations: AE, adverse event; CBC, complete blood count; CDC, centers for Disease Control and Prevention; CHMP, Committee for Human Medicinal Products; CI, confidence interval; DSJI, disposable-syringe jet injection/injector; EMEA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FE, Fisher's exact; GAVI, Global Alliance for Vaccines and Immunization; GMT, geometric mean titers; HBV, hepatitis B virus; HCV, hepatitis C virus; IM, intramuscular; HIV, human immunodeficiency virus; HI, hemagglutination inhibition; JI, jet injector/injection; mm, millimeter; MUNJI, multi-use-nozzle jet injector; NA, not applicable; N–S, needle–syringe; PATH, Program for Appropriate Technology in Health; SAE, serious adverse event; TIV, trivalent (inactivated) influenza vaccine; URI, upper respiratory infection; USAID, United States Agency for International Development; WHO, World Health Organization.

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doi:10.1016/j.vaccine.2011.09.097

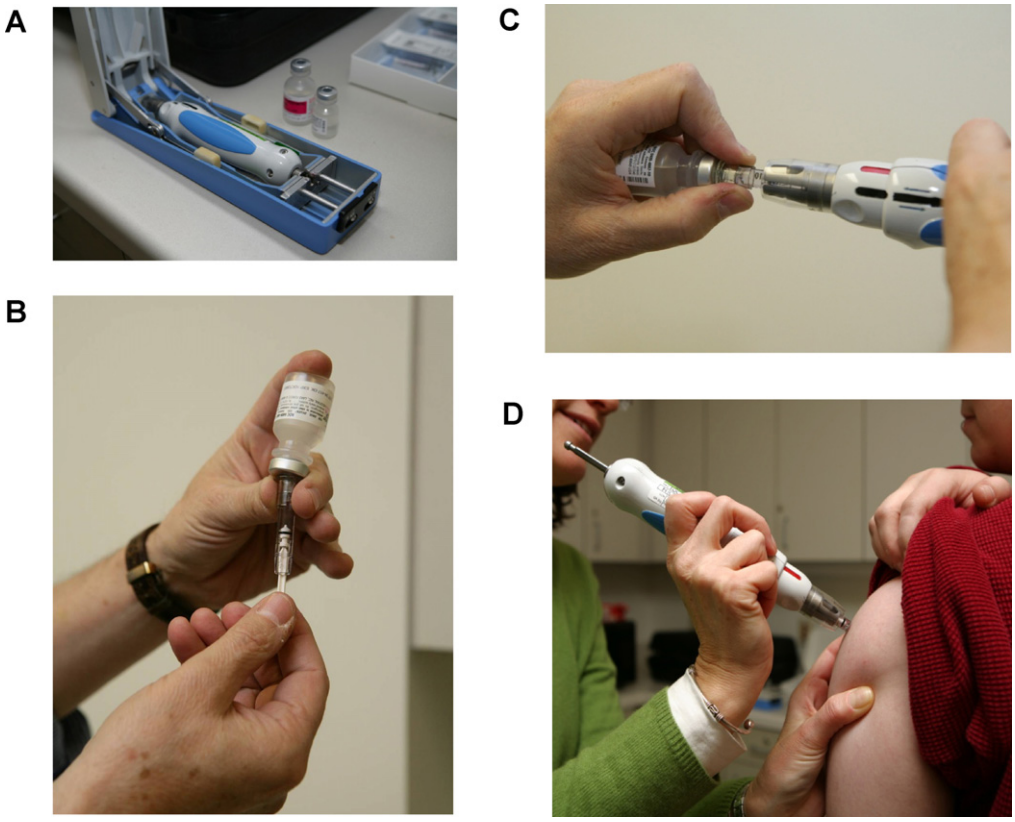

Fig. 1. (A) The LectraJet® M3 RA in its combination storage case and reset station. Upon closing in reset mode, the metal spring of the device is compressed to power the next injection. (B) Manual filling of the LectraJet syringe using a sterile vial adaptor. (C) Engagement of the filled syringe to the injector, before removal of the vial and vial adaptor, which can also be separated beforehand. (D) The injection is activated when the device reaches a pre-set pressure upon application against the limb.

2. Methods

2.1. Subjects

Healthy male and female volunteers aged 18–49 years were recruited from the Baltimore/Washington, DC area for this randomized, controlled, double-masked clinical trial. Volunteers were required to be in good health as evidenced by medical history and physical examination, if indicated. Ineligible were those who received an influenza vaccine in the 2008–2009 or 2009–2010 influenza seasons, received a live-attenuated vaccine within 30 days prior to enrollment or a killed vaccine within 14 days prior to enrollment, were dependent on alcohol or illicit drugs, or were females of childbearing potential with a positive pregnancy test. There were no restrictions on race, ethnic origin, religion, or any social or economic qualifications. Volunteers who satisfied eligibility criteria were randomly allocated into two groups of 30 each to receive licensed, seasonal TIV, either by conventional N–S or DSJI. Investigational Review Board approval, ClinicalTrials.gov registration (identifier NCT00987350), and informed consent of subjects were obtained prior to initiation of enrollment. Good Clinical Practice was utilized throughout the trial.

2.2. Vaccine

All subjects received one 0.5 mL dose from a single lot (U 239 AA) of U.S.-licensed TIV (Fluzone®, Sanofi Pasteur Inc., Swiftwater, PA, USA). The vaccine was non-adjuvanted, formulated as a liquid, and packaged in latex-free 5 mL multi-dose vials containing 10 doses each. It was labeled for the 2009–2010 (Northern Hemisphere) season, and contained 15 μg each of an A/Brisbane/59/2007 (H1N1)-like virus, an A/Brisbane/10/2007 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. The vaccine was stored refrigerated as per manufacturer's instructions with cold-chain maintained and documented throughout the protocol.

2.3. Double masking

Vaccine was injected into the deltoid muscle either by DSJI or N–S. To prevent volunteers from using sound, sight, or feel to identify their study group, during vaccination, the vaccinees: (1) wore ear earphones playing music loud enough to mask the sound of a jet injector, (2) inserted their non-dominant arm through a medical screen that blocked their vision of the injection event and (3) had the needle inserted through the center of a plastic hollow ring held against the skin for those receiving vaccine by N–S. The ring's diameter was equal to the nozzle of the jet injector syringe, in order to mimic contact by the DSJI syringe. Randomization was performed by an unmasked statistician who provided the allocation code to an unmasked vaccinator not involved in subsequent clinical or immunologic assessments.

2.4. Delivery

Vaccinations by the LectraJet® DSJI (Fig. 1) were performed in accordance with its *Instructions for Use* provided by its manufacturer (D'Antonio Consultants International, Inc., East Syracuse, NY, USA). To use the LectraJet®, the vaccinator manually operates a separate "reset" station which provides mechanical advantage to compress the injector's metal spring (Fig. 1A). Vaccine is loaded into the syringe by attaching it via an adaptor to the vaccine vial, pulling back on its plunger to fill its chamber, then breaking off the distal end of the plunger (Fig. 1B). The filled syringe is then inserted into the injector until its grasping jaws lock onto the flanges of the