Safety of live attenuated influenza vaccine in atopic children with egg allergy

Paul J. Turner, FRACP, PhD,[a,b,c] Jo Southern, PhD,[b] Nick J. Andrews, PhD,[b] Elizabeth Miller, FRCPath,[b] and Michel Erlewyn-Lajeunesse, DM,[d] on behalf of the SNIFFLE Study Investigators* *London and Southampton, United Kingdom, and Sydney, Australia*

Background: Live attenuated influenza vaccine (LAIV) is an intranasal vaccine recently incorporated into the United Kingdom immunization schedule. However, it contains egg protein and, in the absence of safety data, is contraindicated in patients with egg allergy. Furthermore, North American guidelines recommend against its use in asthmatic children.
Objective: We sought to assess the safety of LAIV in children with egg allergy.
Methods: We performed a prospective, multicenter, open-label, phase IV intervention study involving 11 secondary/tertiary centers in the United Kingdom. Children with egg allergy (defined as a convincing clinical reaction to egg within the past 12 months and/or >95% likelihood of clinical egg allergy as per published criteria) were recruited. LAIV was administered under medical supervision, with observation for 1 hour and telephone follow-up 72 hours later.
Results: Four hundred thirty-three doses were administered to 282 children with egg allergy (median, 4.9 years; range, 2-17 years); 115 (41%) had experienced prior anaphylaxis to egg. A physician's diagnosis of asthma/recurrent wheezing was noted in 67%, and 51% were receiving regular preventer therapy. There were no systemic allergic reactions (upper 95% CI for population, 1.3%). Eight children experienced mild self-limiting symptoms, which might have been due an IgE-mediated allergic reaction. Twenty-six (9.4%; 95% CI for population, 6.2% to 13.4%) children experienced lower respiratory tract symptoms within 72 hours, including 13 with parent-reported wheeze. None of these episodes required medical intervention beyond routine treatment.
Conclusions: In contrast to current recommendations, LAIV appears to be safe for use in children with egg allergy. Furthermore, the vaccine appears to be well tolerated in children with a diagnosis of asthma or recurrent wheeze. (J Allergy Clin Immunol 2015;136:376-81.)

Key words: *Egg allergy, live attenuated influenza vaccine, asthma, recurrent wheezing, safety*

Egg allergy is one of the most common food allergies in childhood, with an estimated prevalence of at least 2% in preschool children.[1] Influenza vaccines generally contain egg protein (including ovalbumin) because the vaccine virus is cultured in hen's eggs; only vaccines with an ovalbumin concentration of less than 2 μg/mL are currently approved by the United Kingdom (UK) national regulator. In theory, patients with egg allergy might be at increased risk of an allergic reaction to influenza vaccines. In recent years, inactivated influenza vaccines (IIVs) with very low or no ovalbumin content have become available. Observational studies have confirmed the safety of the parenteral IIV in children with egg allergy, including those with a history of previous anaphylaxis to egg,[2,3] and have led to a relaxation of contraindications relating to egg allergy in some guidelines.[4-6]

A trivalent live attenuated influenza vaccine (LAIV) administered through the intranasal route has been available in the United States for several years and received approval for use in Europe in 2010. The vaccine has high efficacy against influenza in children aged 2 to 17 years,[7,8] with a similar safety profile to IIV in children without egg allergy.[9-14] LAIV is also grown in hen's eggs and contains egg proteins. Until recently, there were no published data on the safety of LAIV in children with egg allergy, and thus its use in this population has been contraindicated.

Authorities in North America recommend annual influenza vaccination in children from 2 to 8 years of age, preferably with LAIV.[6] LAIV is not licensed for use in children less than 2 years of age because of an increased incidence of wheezing in this age group after immunization.[10,15] This effect has not been seen in

From [a]the Section of Paediatrics (Allergy & Immunology) and MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, Imperial College London; [b]the Immunisation, Hepatitis and Blood Safety Department, Public Health England, London; [c]the Division of Paediatrics and Child Health, University of Sydney; and [d]the Department of Paediatric Allergy & Immunology, University Hospital Southampton NHS Foundation Trust, Southampton.

*The SNIFFLE Study Investigators are Christine Doyle, George Du Toit, Michel Erlewyn-Lajeunesse, Roisin Fitzsimons, Paul T. Heath, Stephen M. Hughes, Louise Michealis, Jürgen Schwarz, Matthew D. Snape, Gary Stiefel, Huw M. Thomas, and Paul J. Turner.

This report is independent research commissioned and funded by the Department of Health Policy Research Programme (National Vaccine Evaluation Consortium, 039/0031). The views expressed in this publication are those of the authors and not necessarily those of the Department of Health. The study received additional local support through the NIHR Clinical Research Networks, with additional funding for a Scottish site from Health Protection Scotland. P.J.T. and M.E.-L had financial support from the Department of Health for the submitted work. P.J.T. is a recipient of a Clinician Scientist award from the UK Medical Research Council (grant MR/K010468/1) and is supported by the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre and the MRC–Asthma UK Centre in Allergic Mechanisms of Asthma.

Disclosure of potential conflict of interest: P. J. Turner has received research support from the United Kingdom Department of Health, the UK Medical Research Council, and the National Institute for Health Research. M. Erlewyn-Lajeuness has received support for attendance at scientific meetings from Allergy Therapeutics, ALK-Abelló, MEDA Pharmaceuticals, and Thermo Fisher. The rest of the authors declare that they have no relevant conflicts of interest.

ClinicalTrials.gov registration NCT01859039, European Clinical Trials database registration 2013-002031-26.

Received for publication November 25, 2014; revised December 19, 2014; accepted for publication December 23, 2014.

Available online February 13, 2015.

Corresponding author: Paul J. Turner, FRACP, PhD, Section of Paediatrics (Allergy & Immunology), Imperial College London, Norfolk Place, London, W2 United Kingdom. E-mail: p.turner@imperial.ac.uk.

0091-6749

http://dx.doi.org/10.1016/j.jaci.2014.12.1925

Abbreviations used
BTS: British Thoracic Society
IIV: Inactivated influenza vaccine
IQR: Interquartile range
LAIV: Live attenuated influenza vaccine
SIGN: Scottish Intercollegiate Guidelines Network
UK: United Kingdom

older children,[11,15,16] even in those with pre-existing asthma and wheeze,[9] a finding confirmed in postmarketing surveillance data.[12,13] Nonetheless, current guidance from the US Centers for Disease Control and Prevention recommends against using LAIV in children less than 5 years of age with asthma or an episode of wheezing in the previous year.[6]

In 2013, the UK introduced annual influenza immunization using LAIV into the National Immunization Schedule for children.[17] Given that the rate of egg allergy in this age group is estimated to be 2.5%, we estimate (on the basis of UK 2013 population data) that there are 60,000 children in this age group for whom LAIV is contraindicated because of a diagnosis of egg allergy. Therefore egg allergy is a significant barrier to successful implementation of the immunization program, resulting in a requirement to vaccinate children with egg allergy with IIV administered by means of injection (typically in the hospital environment), something which is less acceptable to families and would incur significantly higher health costs. As a result, we sought to assess the safety of LAIV in children with egg allergy to provide data to inform an evidence-based consideration of a change to current guidelines.

METHODS

We conducted a phase IV open-label study of LAIV in children with egg allergy during the UK influenza season (September 2013 to January 2014) across 12 hospital-based allergy centers in the UK. Study participants were recruited locally from allergy clinics. Eligible participants were aged 2 to 17 years with (1) IgE-mediated food allergy to egg, which was defined as a positive food challenge result to egg within the last 12 months under medical supervision; (2) a previous convincing clinical reaction to egg within the past 12 months with evidence of current sensitization on the basis of a positive skin prick test response or serum-specific IgE level to egg white; or (3) evidence of current sensitization consistent with a greater than 95% likelihood of clinical egg allergy, as per published criteria.[18] Patients with a history of prior anaphylaxis to egg or a history of severe but stable asthma were not excluded. Anaphylaxis was defined by using World Allergy Organization criteria.[19] Asthma was classified according to current therapy at the time of immunization using the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines.[20] Skin prick testing was performed in all participants before inclusion according to published guidelines to confirm sensitization to egg (egg white extract; ALK-Abelló, Hørsholm, Denmark) and detect sensitization to potential aeroallergens. Testing and vaccination were deferred if participants had received an antihistamine within the previous 4 days. Participants were excluded if they had previously required invasive ventilation for an anaphylactic reaction to egg, had severe unstable asthma, or had a contraindication to LAIV, such as a prior allergic reaction to a vaccine component (other than egg) or current salicylate therapy or had experienced significant immunocompromise. Vaccination was deferred in participants with acute febrile illness or evidence of increased asthma symptoms for at least 2 weeks after symptom resolution.

The study was approved by the West Midlands–Edgbaston Research Ethics Committee (13/WM/0231), and the parent/guardian of each participant provided written informed consent. Children older than 8 years were encouraged to provide their own assent. The study sponsor was the University Hospital Southampton NHS Foundation Trust (study no. RHM CHI0659). This study was registered with ClinicalTrials.gov (NCT01859039) and the European Union Clinical Trials Register (EudraCT 2013-002031-26).

Procedures

Participants had baseline parameters (blood pressure, heart rate, respiratory rate, and oxygen saturation) measured before LAIV administration, with clinical respiratory and dermatologic assessment at the same time. LAIV (Fluenz [marketed as Flumist in North America] produced for the 2013-2014 influenza season; AstraZeneca, London, UK) was administered into the nasal airway according to the approved summary of product characteristics (ie, 0.1 mL per nostril) in either the allergy day case or clinical research unit at each hospital site. Participants were observed for at least 1 hour for symptoms of local or systemic allergic reactions, as defined by international consensus.[21] Clinical observations were recorded for 60 minutes after vaccine administration, along with symptom scoring (total ocular and nasal symptom score).[22] In one center a subset of patients underwent acoustic rhinometry, an objective assessment of nasal airway patency before and 10 minutes after LAIV administration, as previously described.[23] Emergency contact details were provided for parents to seek advice in the event of any concerns after vaccination. Parents were contacted by telephone after a minimum of 72 hours to detect any delayed adverse reaction.

Participants who had not received immunization with nonpandemic influenza vaccine in previous years were offered a second dose of LAIV at least 4 weeks later in line with the product recommendations.

Outcomes

The primary outcome was the incidence of allergic reaction as an adverse event after immunization occurring within 2 hours of LAIV administration in children with egg allergy. A systemic allergic reaction (anaphylaxis) was defined according to the Brighton Collaboration case definition.[24] Secondary outcomes were as follows: incidence of delayed symptoms occurring up to 72 hours after LAIV administration; incidence of adverse events of nonallergic cause after LAIV administration; and change in nasal airway patency in children who underwent acoustic rhinometry as an additional assessment. The causality of all adverse events was confirmed by an independent data monitoring committee in conjunction with the local study team.

Statistical analyses

Analyses were planned prospectively and detailed in a statistical analysis plan. The incidence of reactions to LAIV (both immediate and delayed) was estimated with 2-sided exact 95% CIs. For subgroup analyses, incidences of reactions were compared between different cohorts by using a 2-sided Fisher exact test. Sample size was considered with respect to a historical comparison and also based on the precision around an estimate of zero. If there were no allergic reactions in a sample size of 300, then this would provide confidence (based on the upper end of the 2-sided 95% CI) that the true rate of allergic reaction to LAIV in children with egg allergy within the population is no more than 1.2%. The analysis data set was as treated and with relevant safety data measured.

RESULTS

Two hundred eighty-two children with egg allergy were enrolled in the study and received at least 1 dose of LAIV between September 2013 and January 2014. The median age of the cohort was 4.9 years (range, 2-17 years; interquartile range [IQR], 3-8 years), and 185 (66%) were male. A total of 433 doses of LAIV were administered to 282 children, 64 with prior influenza vaccination and 218 vaccine-naive children, as depicted in Fig 1. One hundred fifty-one children received a second dose of LAIV 4 weeks later. The reasons for only a single dose of LAIV being administered in the remainder are shown in