Title	Quantitative and qualitative analysis of antibody response after dose sparing intradermal 2009 H1N1 vaccination
Author(s)	Hung, IFN; Levin, Y; To, KKW
Citation	Vaccine, 2012, v. 30 n. 17, p. 2707-2708
Issued Date	2012
URL	http://hdl.handle.net/10722/157685
Rights	NOTICE: this is the author's version of a work that was accepted for publication in Vaccine. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in Vaccine, 2012, v. 30 n. 17, p. 2707-2708. DOI: 10.1016/j.vaccine.2011.12.069

Quantitative and qualitative analysis of antibody response after dose sparing intradermal 2009 H1N1 vaccination

Ivan FN Hung[1,2], Yotam Levin[3], Kelvin KW To[2]

Department of Medicine, the University of Hong Kong, Queen Mary Hospital, Hong Kong Special Administrative Region, China[1]

State Key Laboratory for Emerging Infectious Diseases, Carol Yu's Centre for Infection and Division of Infectious Diseases, the University of Hong Kong, Queen Mary Hospital, Hong Kong Special Administrative Region, China[2]

NanoPass Technologies Ltd, Israel[3].

The 2009 pandemic influenza has provided a unique opportunity to learn about influenza. Dose-sparing intradermal vaccination has been found to be effective in seasonal influenza [1]. However, this strategy has not been tested for the pandemic influenza. We therefore performed a prospective, randomized, open-label, single-centre trial from January to March 2010, to compare the safety and immunogenicity between conventional full-dose intramuscular (IM) and low-dose (20%) intradermal (ID) immunizations of the monovalent 2009 H1N1 vaccine in chronically ill adults.

Patients were randomized to receive a single low-dose (3µg hemagglutinin) ID vaccination or a single full-dose (15µg) IM vaccination. The vaccine used was Panenza® (Sanofi-Pasteur, France), a monovalent inactivated, non-adjuvanted vaccine formulated to contain 15µg of hemagglutinin of influenza A/California/07/2009 virus. Antibody titers were measured using hemagglutination-inhibition (HAI) and microneutralization (MN) assays according to standard methods [2], at baseline, 21 and 42 days after vaccination. Avidity testing was performed by comparing the optical density after urea treatment in an ELISA assay [3]. Safety was assessed by the vaccinees completing the immediate adverse event checklist and a 7-day diary.

A total of 37 subjects (ID:18 and IM:19) were enrolled. Two subjects in the IM group were lost to follow-up. Baseline demographics between the two groups were well matched. No deaths or serious adverse events were reported. Local symptom of post vaccination erythema was significantly more common in the ID group while other local and systemic symptoms were reported in similar frequency in both groups. There was no significant difference in seroconversion and seroprotection rates by

either assay (Table 1) between the two groups on day 21 [HAI seroconversion and seroprotection: ID vs. IM: 27.78% vs. 29.41% (p=1.00)] and day 42 [HAI seroconversion and seroprotection: ID vs. IM: 38.89% vs. 35.29% (p=1.00)]. The geometric-mean-titer (GMT) fold increase by HAI on day 21 in both groups met the criteria defined by the Committee for Proprietary Medicinal Products (CPMP) [GMT fold increase value (95% C.I.): ID vs. IM: 11 (-3.71-25.71) vs. 6.53 (2.12-10.94) (p=1.00)]. There was no correlation between post-vaccination erythema and subsequent seroconversion/ seroprotection rate on day 21 or 42 ($p>0.05$). Antibody avidity testing (Table 1) showed no significant difference between the two groups, and between the day 21 and 42 samples.

This is the first intradermal 2009 H1N1 vaccine evaluation. Data from this study suggested that immunogenicity of the monovalent H1N1 2009 vaccine was lower than previously published results for similar unadjuvanted 15μg split virus vaccines [4]. This could be attributed to population selection (patients with chronic diseases or elderly) or high pre-immunization antibody response [5]. Adjuvants or booster dose should be considered to generate satisfactory immunogenicity [4]. The limitation of this study is the lack of appropriate sample size secondary to the widely report of an unrelated post vaccinee who developed Guillain-Barre syndrome, discouraging potential vaccinees who may benefit from this vaccine. In conclusion, dose sparing intradermal influenza vaccination is safe and effective and should be encouraged in elderly and immunosuppressed patients. This strategy should be incorporated in the pandemic preparedness plans globally.

(Word count 500)

Acknowledgments

This clinical study was supported by a grant of the Research Fund for Clinical Infectious Diseases, Hong Kong Government. The authors would like to thank Professor Kwok-Yung Yuen, Dr Kwok-Hung Chan, Mr. Patrick Li, Miss Clara Li, Miss Ting Xu and Miss Tin-Yan Wong in assisting this study. The MicronJet devices for intradermal injection were provided by NanoPass Technologies Ltd.

Disclaimer

The second author Yotam Levin would like to declare that he is currently chief executive officer of the NanoPass Technologies Ltd.

References

1. Van Damme P, Oosterhuis-Kafeja F, Van der Wielen M, Almagor Y, Sharon O, Levin Y. Safety and efficacy of a novel microneedle device for dose sparing intradermal influenza vaccination in healthy adults. *Vaccine* 2009;27:454-9.

2. Chan KH, To KK, Hung IF, Zhang AJ, Chan JF, Cheng VC, et al. Differences in the antibody response between individuals with natural infection of and vaccination against pandemic H1N1 2009 influenza. *Clin Vaccine Immunol* 2011;18:867-73.

3. Woo PC, Lau SK, Tsoi HW, Chan KH, Wong BH, Che XY, et al. Relative rates of non-pneumonic SARS coronavirus infection and SARS coronavirus pneumonia. *Lancet* 2004;363:841-5.

4. Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, Bennet J, et al. Response to a monovalent 2009 influenza A (H1N1) vaccine. *N Engl J Med* 2009;361:2405-13.

5. Gulati U, Keitel WA, Air GM. Increased antibodies against unfolded viral antigens in the elderly after influenza vaccination. *Influenza Other Respi Viruses* 2007;1:147-56.

Table 1. Immunogenicity by hemagglutination-inhibition and microneutralization assays

			ID	IM	*P*- value
Hemagglutination-Inhibition					
GMT values (95% CI)		Day 0	7.08 (5.56-9.02)	6.14 (5.2-7.26)	
		Day 21	22.39 (11.25-44.57)	21.63 (11.56-40.46)	
		Day 42	23.27 (11.52-46.97)	17.66 (8.86-35.23)	
CPMP criteria (day 21)	Seroconversion (%)		27.78	29.41	1.00
	Seroprotection (%)		27.78	29.41	1.00
	GMT fold increase value (95% CI)		11 (-3.71-25.71)	6.53 (2.12-10.94)	
CPMP criteria (day 42)	Seroconversion (%)		38.89	35.29	1.00
	Seroprotection (%)		38.89	35.29	1.00
	GMT fold increase value (95% CI)		11.25 (-3.43-25.93)	5.88 (1.58-10.18)	
Microneutralization					
GMT values (95% CI)		Day 0	12.11 (9.12-16.11)	10.84 (8.77-13.43)	
		Day 21	22.39 (12.39-40.46)	25.47 (12.79-50.85)	
		Day 42	25.12 (13.46-46.88)	29.92 (15.60-57.54)	
CPMP criteria (day 21)	Seroconversion (%)		16.67	29.41	0.443
	Seroprotection (%)		27.78	29.41	1.00
	GMT fold increase value (95% CI)		3.81 (0.14-7.47)	5.54 (1.21-9.87)	
CPMP criteria (day 42)	Seroconversion (%)		22.22	35.29	0.315
	Seroprotection (%)		38.89	35.29	1.00
	GMT fold increase value (95% CI)		4.06 (1.28-6.83)	4.97 (2.02-7.92)	
Avidity Testing					
Mean Antibody Index (SEM)		Day 21	18.97 (1.99)	15.93 (8.1)	0.285
		Day 42	17.07 (1.35)	16.78 (2.35)	0.912

ID: intradermal group; IM: intramuscular group. GMT: geometric mean titer; CPMP: Committee for Proprietary Medicinal Products; SEM: standard error of the mean CPMP guideline: at least one of the following criteria must be met for the viral strain in the vaccine: GMT fold increase >2.5, seroconversion rate >40% and seroprotection rate > 70%