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A pilot randomized study to assess immunogenicity, reactogenicity, safety and tolerability of two human papillomavirus vaccines administered intramuscularly and intradermally to females aged 18–26 years☆

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ABSTRACT

Intradermal administration of human papillomavirus (HPV) vaccines could be dose-sparing and cost-saving. This pilot randomized study assessed Cervarix® and Gardasil® administered either intramuscularly or intradermally, in different doses (full-dose or reduced to 20%) by different methods (needle and syringe or PharmaJet needle-free jet injection device). Following an initial reactogenicity study of 10 male subjects, sexually naïve women aged 18–26 years were randomized to the eight study groups to receive vaccine at 0, 2 and 6 months. 42 female subjects were enrolled and complete data were available for 40 subjects. Intradermal administration of either vaccine raised no safety concerns but was more reactogenic than intramuscular administration, although still tolerable. All subjects demonstrated a seroconversion (titre ≥ 1:320) by Day 95. Further evaluation of intradermal HPV vaccination and its potential for cost reduction in resource poor settings is warranted.

1. Introduction

In 2008, there were about 530,000 new cases of cervical cancer, and about half this number (275,000) died of the disease worldwide [1]. The age-standardized incidences of new cases and mortality were 15 and 8 per 100,000, respectively. Worldwide, cervical cancer ranked third among cancers in women, just following breast cancer (1.3 million new cases) and colorectal cancer (0.57 million new cases) in 2008 [2]. Approximately 80% of cervical cancer mortality occurs in the developing world where comprehensive and effective, population-level cervical cancer screening programmes are often not available. Although about 15 genotypes of human papillomavirus (HPV) have been causally associated with cervical cancer, HPV16 and HPV18 are responsible for about 70% of cases.

Two vaccines against HPV16 and HPV18 are licensed and have been introduced into the national immunization programmes of some countries. A bivalent HPV16/18 vaccine adjuvanted with 3-O-desacyl-4′-monophosphoryl lipid A (ASO4) (Cervavix®, GlaxoSmithKline) showed efficacy of 98% (CI 88–100) against cervical intraepithelial neoplasia 2+ with a probable causality to HPV16 or HPV18 [3]. A quadrivalent vaccine against HPV types 6, 11, 16, and 18 (Gardasil®, Merck Sharp & Dohme Ltd.) showed an efficacy of 98% (CI 86–100) in the per-protocol susceptible population for the prevention of cervical intraepithelial neoplasia grade 2 or 3 and adenocarcinoma in situ related to HPV-16 or HPV-18 [4]. Both vaccines contain aluminium hydroxide. These vaccines have the potential to prevent a significant proportion of cervical cancer globally but cost is likely to limit rapid widespread introduction.

Abbreviations: ASO4, 3-O-desacyl-4′-monophosphoryl lipid A; DMEM, Dulbecco's modified Eagle's medium; FBS, fetal bovine serum; GMT, geometric mean titre; HEPES, 1% 4-[2-hydroxyethyl]-1-piperazine ethanesulfonic acid; HPV, human papilloma virus; ID, intradermal; IM, intramuscular; NAM, neutralization assay medium; PBNA, pseudovirion-based neutralization assay; SAE, serious adverse events; SEAP, secreted alkaline phosphatase.

☆ Clinical trial was registered with Australian New Zealand Clinical Trials Registry (ACTRN12608000339358).

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The skin is an excellent immune organ and has a high density of epidermal Langerhans and dermal dendritic cells efficient in antigen uptake, providing the potential for lower dosages of antigen to produce immunity [5]. Intradermal administration of vaccines will present antigen to macrophages and dendritic cells with the potential to produce adequate levels of serum antibodies with lower vaccine dosages [6]. This route of administration has been evaluated for a number of vaccines including influenza, measles, cholera, typhoid, rabies, hepatitis B and polio [5,7,8]. A favourable immune response has also been demonstrated for DNA- and peptide-based therapeutic HPV vaccines when administered via the intradermal route [9–11]. Although the intradermal administration route may be associated with less pain at the time of administration, subjects may experience an increased likelihood of subsequent local reactions such as redness and induration due to inflammation at the injection site. Hyperpigmentation has been reported in some subjects after intradermal administration of hepatitis B vaccine [12], which resolved by 18 months [13]. A meta-analysis of intradermal versus intramuscular hepatitis B vaccine in patients with chronic kidney disease noted that local reactions (itchiness and soreness) and systemic adverse events (arthralgia, general pruritus, low-grade fever, headache and nausea) occurred, but they were mild and not found to be unacceptable [8]. Comparable immunogenicity to full-dose intramuscular influenza vaccine was demonstrated with a dose reduced to 20% of the full-dose given intradermally [14]. Intradermal administration can be achieved with fine gauge needles (Mantoux injection technique), the "bifurcated needle" developed for smallpox vaccination, old multi-use nozzle injectors, new disposable syringe jet injectors such as the Biojector® 2000, microinjection systems, transdermal delivery and transdermal microneedle arrays, and the PharmaJet device used in this study [5].

This pilot study assessed immunogenicity, reactogenicity, safety and tolerability of a reduced-dose intradermal administration of HPV vaccines (Cervarix® and Gardasil®) for healthy females aged 18–26 years, so as to determine whether a larger study would be justified.

2. Methodology

2.1. Initial open label reactogenicity assessment of male subjects

To ensure that no unexpectedly severe reactions occurred with either vaccine administered intradermally, an initial reactogenicity assessment was undertaken with 10 adult male subjects aged 18–46 years. After signing an informed consent, subjects were assessed to ensure that they were generally healthy with no pre-existing medical conditions and then blood was taken for HPV antibody status (Table 1a). Subjects were informed that a single dose of HPV vaccine given intradermally would not be anticipated to provide protection against HPV infection. Using a sealed envelop containing a random number, subjects were selected to receive either Cervavix® or Gardasil®. A 20% dose (0.1 mL) of either vaccine was given intradermally with a tuberculin syringe and 29-gauge needle into the skin over the deltoid muscle of either arm. Photographs were taken immediately after administration. Study procedures at each of the study visits are detailed in Table 1a. Subjects with persisting injection site reactions had additional review visits.

2.2. Main female study

Female subjects aged 18–26 years were enrolled. Inclusion criteria included being generally healthy with no pre-existing medical conditions, agreement to keep a record of symptoms after each vaccination and to be sexually naïve at the time of enrollment. Exclusion criteria included a titre of more than 1:80 for either HPV16 or HPV18 serum neutralizing antibodies at enrollment, allergy to any vaccine component, received blood products or components during the previous 6-months, known immune or coagulation disorder, received any inactivated vaccine product within the 14 days before enrollment or any live vaccine product within 21 days before enrollment.

As part of the consenting process, subjects were shown the photographs of the skin reactions experienced by the males participating in the initial reactogenicity assessment study. After signing informed consent and undergoing a health check, the female subjects had blood taken for screening serum antibody to HPV16 and HPV18 (Table 1b). At Visit 2, subjects testing negative for both HPV16 and HPV18 were randomized into one of the eight study groups by selecting a sealed envelope (Table 2). After completing a health check questionnaire, the 1st vaccination was given and subjects were observed for 30 min. Full blinding was not undertaken as the study involved three clearly identifiable routes of administration. However subjects were not informed which vaccine or which intramuscular dose they received. The nurses involved in administrating the majority of the vaccines were not involved with the follow-up of subjects. Study procedures at each of the study visits are detailed in Table 1b.

2.3. Safety and reactogenicity assessments

Both male reactogenicity study and main female study used the same safety and tolerability assessments. Subjects ranked, on a scale of 1–10 (1 = not at all painful, 10 = extremely painful), how painful the vaccination was at the time of administration. Subjects recorded their oral temperature each evening before bedtime for 7 days, and injection site reactions and adverse effects were elicited for 14 days following each vaccination.

The following information was sought in the "Injection Site Reaction Diary Card": pain at the injection site (does not interfere with activity, interferes with activity, prevents daily activity); tenderness at the injection site (mild discomfort to touch; discomfort with movement, significant discomfort at rest); redness of the injection site (maximum diameter in millimetres and presence of skin peeling); swelling of surrounding skin (maximum diameter in millimetres, does not interfere with activity, interferes with

Table 1a
Procedure schedules for the open label reactogenicity assessment of male subjects.

Visit number	Time	Procedures
Visit 1	Day 1	Consent, medical examination, blood taking, randomization of all eligible subjects, vaccination Cervavix® or Gardasil®, vaccine site photographed, subjects observed for 30 min after vaccination. Subjects given a digital thermometer to check oral temperatures and a plastic ruler to measure injection site reactions
Visit 2	7 days after Visit 1	Diary card reviewed, vaccine site photographed
Visit 3	30 days after Visit 1	Diary card reviewed, blood taking, vaccine site photographed
Visit 4	60 days after Visit 1	Review of 8 subjects with persistent injection site reaction at Visit 3
Visit 5	90 days after Visit 1	Review of 2 subjects with persistent injection site reaction at Visit 4
Visit 6	180 days after Visit 1	Review of 1 subject with persistent injection site reaction at Visit 5