Rev Colomb Cancerol. 2013;**17(3)**:103-110

Revista Colombiana de Cancerología

www.elsevier.es/cancerologia

ORIGINAL ARTICLE

Evaluation of the immune response to human papillomavirus types 16, 18, 31, 45 and 58 in a group of Colombian women vaccinated with the quadrivalent vaccine

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Received 21 December 21 2012; accepted 2 July 2013

KEYWORDS
Papillomavirus Vaccines;
Immunity;
Seroprevalence

Abstract
Objective: To analyze whether the immune response to HPV-16, -18, -31, -45 and -58 capsids in women vaccinated with the quadrivalent vaccine induces cross-reactivity against other HPV virus-like particles (VLPs).
Methods: A total of 88 women aged between 18 and 27 years attending the HPV clinic at the *Instituto Nacional de Cancerología* were enrolled and vaccinated against HPV. Follow-up visits were scheduled at months 7, 12, and 24. Samples were collected for cytology, HPV-DNA typing, and detection of HPV antibodies. IgG antibodies were measured by ELISA using HPV-16, -18, -31, -45, and -58 VLPs. HPV-DNA detection was done by GP5+/GP6+PCR-ELISA and HPV typing was performed by Reverse Line-Blot assay.
Results: Pre-vaccination, the seroprevalence of HPV-16, -18, -31, -45, and -58 was 39%, 31.7%, 15.9%, 31.7%, and 23.2%, respectively. One month post-vaccination, the seroprevalence increased close to 100% for all types. At month 24, this response was maintained only for HPV-16 and -18. For HPV-31, -45 and -58, the seroprevalence decreased to below 50%. The prevalence of HPV DNA types 16, 18 and 58 before vaccination was little changed 1 month after vaccination. No new infections were observed at 24 months. For HPV-16 and -18 related types, no differences were observed before vaccination and at month 24. For other high-risk HPV types, the prevalence increased 18 months post-vaccination (15.5%) compared with pre-vaccination (9.8%).

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Conclusion: Immune response to all HPV types increased after vaccination, but this increase was maintained only for HPV-16 and -18. These results suggest a possible cross-reactivity against HPV types 31, 45 and 58, but this cross-reactivity wanes with time.

PALABRAS CLAVE
Vacunas contra Papillomavirus;
Inmunidad;
Seroprevalencia

Evaluación de la respuesta inmune hacia el virus del papiloma humano tipos 16, 18, 31, 45 y 58 en un grupo de mujeres colombianas que recibieron la vacuna tetravalente

Resumen
Objetivo: Analizar si la respuesta inmune hacia las cápsides del VPH tipos 16, 18, 31, 45 y 58 en mujeres que recibieron la vacuna tetravalente induce reactividad cruzada hacia otros tipos virales.
Métodos: Ochenta y ocho mujeres entre 18 y 27 años, asistentes al Grupo VPH del Instituto Nacional de Cancerología, recibieron la vacuna de VPH. Visitas de seguimiento en los meses 7, 12 y 24. Se tomaron muestras para prueba de Papanicolaou, tipificación de VPH y detección de anticuerpos. Los anticuerpos se detectaron por ELISA, usando VLP-VPH. La detección del ADN-VPH se realizó por Reverse Line Blot.
Resultados: Prevacunación, la seroprevalencia de VPH tipos 16, 18, 31, 45 y 58 fue de 39, 31,7, 15,9, 31,7 y 23,2%, respectivamente. Al mes 7 aumentó cerca del 100% para todos los tipos. Al mes 24 esta respuesta se mantuvo para VPH tipos 16 y 18. Para VPH tipos 31, 45 y 58 disminuyó por debajo del 50%. La prevalencia de ADN-VPH tipos 16, 18 y 58 tuvo poca variación antes y un mes después de la vacunación. Al mes 24, no se observaron nuevas infecciones. Para VPH tipos 16 y 18, no se observaron diferencias antes ni al mes 24. En otros tipos de HR-VPH aumentó la prevalencia al mes 24 (15,5%), comparada con la prevacunación (9,8%).
Conclusión: Se observó un aumento de la respuesta inmune a todos los tipos de VPH después de la vacunación, pero esta se mantuvo solamente para los VPH tipos 16 y 18. Los resultados sugieren una posible reactividad cruzada contra VPH tipos 31, 45 y 58. Sin embargo, esta reactividad cruzada disminuye con el tiempo.

Introduction

The recognition of an etiologic association between high-risk human papillomavirus (HPV) infection and cervical cancer has promoted the development of prophylactic vaccines for the prevention of HPV infection[1]. To date, two prophylactic HPV vaccines have been developed commercially: *Cervarix*™, from GlaxoSmithKline, is a bivalent vaccine composed of virus-like particles (VLPs) made from recombinant L1 proteins of HPV-16 and -18 and formulated with an adjuvant ASO4, which contains a combination of aluminum hydroxide and the immunostimulant MPL[2] (3-*O*-desacyl-4′-monophosphoryl lipid A). *Gardasil*™, from Merck, is a quadrivalent valent vaccine composed of VLPs from HPV-16, -18, -6, and -11 formulated with an aluminum hydroxyphosphate-based adjuvant[3].

Numerous clinical trials have shown that both vaccines exhibited high prophylactic efficacy (up to 100%) in preventing incident HPV-16 and -18 infections and their associated precancerous lesions[4-12]. These vaccines induce high levels of serum IgG antibodies against VLP HPV-16 and -18, which are up to 1000 times higher than those observed after natural infection. The protection afforded by these vaccines has been demonstrated up to 8.4 years post-vaccination for the HPV 16/18 vaccine[13] and 5 years post-vaccination for the HPV 6/11/16/18 vaccine[11].

It is recognized that the protective efficacy of HPV vaccines is mediated by anti-L1 humoral response[14,15]. These antibodies are predominantly type-specific; however, a weak cross-reactivity has been reported between very closely related types such as HPV 6/11, HPV 18/45 and HPV 16/31[16-20]. Several clinical studies indicate that HPV vaccines may confer protection against some phylogenetically-related HPV types but not against distantly-related types[10,21]. It has been reported that the bivalent (HPV16/HPV18) vaccine induces protection against incident infections and premalignant lesions with HPV-45 (HPV-18-related type) and HPV-31[22-24] (HPV 16-related type). In contrast, for the quadrivalent HPV vaccine, cross-protection against HPV-45 has been reported, but not against CIN1-3 or adenocarcinomas in situ associated with this type (19) Moreover, a modest reduction in HPV-31, -33, -45, -52, -58-related CIN2, CIN3 and AIS has been observed. These findings suggest that vaccination could induce a protective immune response against HPV types not included in the vaccine.

Previous epidemiological studies have shown geographic differences in the prevalence of HPV. In these studies, although HPV16 was the predominant type detected, marked differences were noted in the prevalence of other high-risk HPV types[25-27]. In Colombia, a study of the prevalence and determinants of HPV infection among Colombian women with normal cytology showed wide diversity of HPV