Concomitant Administration of Pneumococcal-23 and Zoster Vaccines Provides Adequate Herpes Zoster Coverage

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Request

Does concomitant administration of pneumococcal-23 and zoster vaccines provide adequate coverage against herpes zoster infections?

Response

BACKGROUND

Streptococcus pneumoniae, the most common cause of community-acquired pneumonia, has been associated with significant morbidity and mortality in the elderly.[1] In 2004, pneumococcal disease was linked to 242,000 hospitalizations, 194,000 emergency department visits, and 16,000 deaths in patients aged 65 years or older in the US.[2] Herpes zoster, another infection with a detrimental impact on the geriatric population, is characterized by an excruciating vesicular rash, complicated in 10% of all cases by postherpetic neuralgia.[1] Approxi-

Author information provided at end of text.

OBJECTIVE: To determine whether concomitant administration of zoster vaccine and polysaccharide pneumococcal-23 vaccine (PPV23) provides sufficient protection against herpes zoster infections.

DATA SOURCES: Literature was retrieved through the Centers for Disease Control and Prevention (CDC) website, PubMed (inception-February 2013), and Scopus (inception-February 2013) using the key words herpes zoster, pneumococcal, vaccine, concomitant, simultaneous administration, Pneumovax, Zostavax, and barriers. In addition, reference citations from publications were used.

STUDY SELECTION AND DATA EXTRACTION: All English-language articles identified from the data sources were evaluated. Two studies evaluating concomitant and nonconcomitant administration of zoster vaccine and PPV23 were included.

DATA SYNTHESIS: Current product labeling recommends a 4-week interval between zoster vaccine and PPV23 administration; however, the Food and Drug Administration (FDA) and the CDC promote concomitant administration to prevent a missed opportunity to vaccinate. This has caused confusion among health care professionals regarding the appropriate timing of these vaccines. A randomized trial that evaluated the immunogenicity of zoster vaccine and PPV23 given together versus separated by at least 4 weeks demonstrated that the varicella zoster virus (VZV) antibody levels of concomitant versus nonconcomitant vaccination groups did not meet noninferiority requirements. However, a large retrospective cohort trial that compared the incidence of herpes zoster infections following concomitant versus nonconcomitant administration of PPV23 and zoster vaccine did not find a statistically significant between-group difference.

CONCLUSIONS: Concomitant administration of zoster vaccine and PPV23 is advocated by the CDC and FDA to improve immunization rates among vaccine-eligible individuals. Since there is no direct evidence that simultaneous administration of zoster vaccine and PPV23 puts patients at increased risk of developing herpes zoster, the vaccines should be given during the same office visit to avoid a missed opportunity to vaccinate against 2 serious diseases.

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mately 1 million patients in the US develop this affliction each year, of which between 1 and 4% will require hospitalization and 96 will die from zoster-related complications.[3]

To combat these serious diseases, 2 vaccines were developed. Pneumovax-23 (polysaccharide pneumococcal-23 vaccine [PPV23], Merck & Co., Inc.), an inactivated vaccine containing 23 serotypes of pneumococcal polysaccharide antigens, was approved in 1983.[4] It has been reported to be 50-85% effective in preventing invasive pneumococcal disease in healthy adults.[2] This vaccine is approved by the Food and Drug Administration (FDA) for the prevention of pneumococcal pneumonia in patients aged 50 years or older and in patients aged 2 years or older who are at increased risk for pneumococcal disease.[5] In contrast, the Centers for Disease Control and Prevention (CDC) recommends routine PPV23 immunization in adults without an underlying medical condition, starting at age 65 years.[6] Zostavax (zoster vaccine, Merck & Co., Inc.), a live vaccine, became commercially available in 2006 for use in patients aged 60 years or older, with a documented efficacy rate of approximately 52%.[7,8] In 2011, the FDA expanded approval for zoster vaccine to include individuals aged 50 years or older.[9] However, the CDC still recommends its use in the original FDA-approved older population.[10] Despite the benefits of vaccination, a 2010 CDC report indicated that only 59.7% of vaccine-eligible adults aged 65 or older received PPV23 and only 14.4% of patients aged 60 years or older received zoster vaccine in the US.[11] The US Department of Health and Human Services promotes a 90% vaccination rate for several vaccines, including PPV23.[12] Simultaneous or concomitant administration, defined by the CDC as giving more than 1 vaccine on the same day, at different anatomic sites, but not combined in the same syringe, is recommended as an effective approach to boosting immunization rates.[12,13] The inability to give multiple vaccines during the same office visit is perceived as a barrier in ensuring adequate protection against vaccine-preventable diseases.

According to the Guidelines for Spacing of Live and Inactivated Antigens by the CDC, an inactivated vaccine (eg, PPV23) and a live vaccine (eg, zoster vaccine) may be given either simultaneously or separately at any interval between doses.[14] This recommendation is based on the assumption that an inactivated vaccine should not interfere with the immune response to either a live or another inactivated vaccine. However, this generalization is extrapolated from various clinical trials that did not evaluate concurrent administration of zoster vaccine and PPV23. Therefore, a blinded, controlled clinical trial was conducted to determine the safety and immunogenicity of zoster vaccine and PPV23 given simultaneously.[1] The trial's primary immunogenicity end points were as follows: (1) the geometric mean titer (GMT) of varicella zoster virus (VZV) antibody at 4 weeks postvaccination, (2) the estimated geometric mean fold rise (GMFR) of VZV antibody from baseline to 4 weeks postvaccination, and (3) the GMT ratio of pneumococcal polysaccharide (PnPs) antibodies between vaccination groups. The GMT ratio for PnPs antibodies was determined to be noninferior between groups, reflecting similar protection against pneumococcal antigens. Although the between-group estimated GMFR of the VZV antibody response met noninferiority standards, the GMT ratio for VZV antibodies (concomitant/ nonconcomitant) did not meet the noninferiority criterion, leading to the assumption that the nonconcomitant group achieved a more robust response to the zoster vaccine. Even though the true clinical significance of this result was unknown, the FDA updated the zoster vaccine and PPV23 product labels in 2009 with the following statement: "Zostavax and Pneumovax23 (pneumococcal vaccine polyvalent) should not be given concurrently because concomitant use resulted in reduced immunogenicity of Zostavax."[15] This updated product labeling required patients to schedule 2 separate office visits to receive these vaccines. Since the need for 2 office visits may result in missed opportunities to vaccinate, another study was conducted to determine whether there was a direct correlation between increased incidence of herpes zoster and the simultaneous administration of zoster vaccine and PPV23.[16] The results of this study led to another change in product labeling for zoster vaccine and PPV23 in 2010 to include the following statement, "Consider administration of the two vaccines [zoster vaccine and PPV23] separated by at least 4 weeks."[17] Despite this revision, in 2011 the FDA supported the simultaneous administration of these vaccines, which has been consistently promoted by the CDC since the approval of zoster vaccine in 2006.[18,19] Based on our experiences in a drug information center, the differences in the product labeling and recommendations from these federal agencies has led to confusion among health care professionals regarding appropriate spacing of zoster vaccine and PPV23. Therefore, this review assesses the only 2 available studies that evaluated the concomitant versus nonconcomitant administration of zoster vaccine and PPV23 to determine whether PPV23 truly interferes with the immunologic response to zoster vaccine and thus needs to be given 4 weeks apart.

Literature Review

A literature search was performed using the CDC website, PubMed (inception-February 2013), and Scopus (inception-February 2013), with the search terms herpes zoster vaccine, pneumococcal, vaccine, concomitant, Food and Drug Administration, Pneumovax, Zostavax, and barriers. References from identified publications were reviewed for relevant information. Two trials were identified that evaluated the concomitant administration of zoster vaccine and PPV23 vaccines in patients aged 60 years or older.

MacIntyre and associates performed a randomized, double-blind, placebo-controlled study that evaluated the safe-

ty and immunogenicity of zoster vaccine administered concomitantly versus nonconcomitantly with PPV23 in patients aged 60 years or older.[1] A primary objective was to determine whether the immunologic response to zoster vaccine, determined by VZV antibody levels at 4 weeks postvaccination in participants who received zoster vaccine and PPV23 concomitantly, was noninferior to the response in those who received sequential dosing. The VZV antibody responses were quantified by the GMT ratio (concomitant/nonconcomitant) and the GMFR. Additionally, the between-group immunologic response to the PPV23 vaccine determined by the GMT ratio of select PnPs antibodies was assessed. A total of 235 patients received both zoster vaccine and PPV23 on day 1 and placebo at week 4, while 236 patients received PPV23 and placebo on day 1 and zoster vaccine at week 4. Blood samples for VZV antibodies were obtained on day 1, week 4, and week 8. The statistical criterion for noninferiority of the VZV antibody response was established as the lower bound value of 0.67 of the 2-sided 95% CI of the VZV antibody GMT ratio. All values of the 95% CI needed to be greater than 0.67 to rule out a clinically significant between-group difference of a 1.5-fold reduction in antibody levels. The estimated GMT values at 4 weeks postvaccination for the concomitant versus the nonconcomitant group were 338 and 484, respectively, whereas the GMT ratio in the concomitant group compared with the nonconcomitant group was 0.70 (95% CI 0.61-0.80). These results did not meet noninferiority requirements since the lower bound value in the confidence interval was not greater than 0.67. However, between-group differences in antibody levels for VZV determined by the GMFR and antibody levels for PnPs determined by the GMT were deemed noninferior. Adverse events were similar between groups. The authors concluded that zoster vaccine and PPV23 should not be given during the same office visit because of the unexpected reduction in the GMT ratio of VZV antibodies in the concomitant group. The differences in the results of outcome measures of VZV antibody levels (GMT vs GMFR) bring into question the clinical significance of these results. Additionally, it is questionable whether the VZV antibody level is really an accurate indicator of herpes zoster susceptibility. An immunology study demonstrated the incidence of herpes zoster infections correlated with a decline in VZV-specific T cell–mediated immunity rather than a reduction in VZV antibody levels.[20] If this is the case, the lower GMT ratio in the concomitant group would not necessarily be associated with an increased risk of herpes zoster infections. Furthermore, the specific antibody level that provides adequate protection against herpes zoster infections has not been established.[8] Therefore, MacIntyre and associates' recommendation against concomitant zoster vaccine and PPV23 administration based solely on VZV antibody titer results may not be relevant.

To clarify whether concurrent administration of zoster vaccine and PPV23 would cause a clinically significant reduction in the immunogenic effect of the zoster vaccine, Tseng and colleagues conducted a large retrospective cohort trial.[16] The primary objective was to determine whether concomitant administration of these vaccines was associated with an increased incidence of herpes zoster. Patients aged 60 years or older who used the Kaiser Permanente Southern California (KPSC) Healthcare System from January 2007 to June 2010 were included. A total of 7179 patients were in the nonconcomitant group, which received the PPV23 vaccine 365 to 30 days prior to administration of zoster vaccine, and 7187 patients were in the concomitant group, which received the vaccines on the same day. The follow-up period for determining the occurrence of herpes zoster infection started the day zoster vaccine was given and ended the date of herpes zoster occurrence, termination of KPSC membership, or June 30, 2010, whichever happened earliest. During the study period, 56 cases of herpes zoster were identified in the concomitant group compared with 58 cases in the nonconcomitant group. The average follow-up time from vaccination administration to herpes zoster occurrence ranged from 1.72 to 1.79 years. The hazard ratio comparing the incidence rate of herpes zoster in the concomitant versus nonconcomitant cohort was 1.19 (95% CI 0.81-1.74). The between-group cumulative risk for herpes zoster was not statistically significant ($p = 0.76$). The authors concluded that simultaneous administration of zoster vaccine and PPV23 was not associated with an increased incidence of herpes zoster. A potential drawback of this study was that the low occurrence of herpes zoster cases may have impaired the ability to detect a between-group difference. Additionally, misclassification of herpes zoster cases because of potential coding errors in the electronic medical record system could have affected the results. A major limitation of this study was that the between-group VZV antibody titer levels were not assessed. It would have been helpful to know whether these levels were comparable to determine whether VZV antibody levels actually affect susceptibility to herpes zoster. However, the authors stated that higher VZV antibody levels are not a true measure of protection against herpes zoster and may actually be associated with a more severe form of the disease since they reflect more extensive VZV replication. In fact, another study found that high VZV antibody levels were linked to greater herpes zoster severity and increased occurrence of postherpetic neuralgia.[21]

Summary

Morbidity and deaths associated with vaccine-preventable infections continue to affect the elderly population, and immunization rates among older adults still fall short of goals established by the Department of Health and Human Services. Simultaneous administration of multiple vaccines during an office visit is recognized as an important strategy in

improving the rate of vaccination. Although the current product labeling for zoster vaccine and PPV23 recommends separating administration by at least a 4-week interval, the CDC and the FDA support coadministration to help boost immunization rates. Two key clinical trials have evaluated the impact of concomitant administration of zoster vaccine and PPV23. The first study demonstrated that concomitant administration resulted in lower VZV antibody levels, but this was not directly associated with an increased risk of herpes zoster. However, other trials have demonstrated that higher VZV antibody levels may not correlate with clinical efficacy and may actually be linked to a more severe herpes zoster disease state. Additionally, a large retrospective trial did not find an association between concomitant administration of zoster vaccine and PPV23 and the incidence of herpes zoster. Since there is a lack of direct evidence demonstrating that simultaneous administration of zoster vaccine and PPV23 puts patients at increased risk of developing herpes zoster, concomitant administration is recommended to avoid a missed opportunity to provide protection against 2 serious diseases.

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EXTRACTO

La Administración Concomitante de la Vacuna Pneumococcal-23 y la Vacuna Zoster Provee una Cobertura Adecuada Contra Herpes Zoster

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OBJETIVO: Determinar si la administración concomitante de la vacuna zoster (VZ) y la vacuna de Polisacáridos Pneumococcal-23 (PPV23) pueden proveer protección suficiente contra infecciones de herpes zoster (HZ).

FUENTES DE DATOS: La literatura encontrada fue recuperada a través de la página web del Centro para el Control y Prevención de Enfermedades (CDC), PubMed (desde el ini cio hasta febraro 2013), y Scopus (desde el inicio hasta febraro 2013) utilizando las siguientes palabras claves: herpes zoster, pneumococcal, vacuna, concomitante, administración simultánea, Pneumovax, Zostavax, y barreras. En adición, referencias citadas de publicaciones fueron utilizadas.

SELECCIÓN DEL ESTUDIO Y EXTRACCIÓN DE DATOS: Todos los artículos en inglés identificados de las fuentes de datos fueron evaluadas. Dos estudios evaluando la administración concomitante y no concomitante de ZV y PPV23 fueron incluídos.

SÍNTESIS DE LA DATA: La información del producto actual recomienda un intervalo de 4 semanas entre VZ y PPV23, sin embargo; la Administración de Alimentos y Medicamentos (FDA) y el CDC promueven la administración concomitante con el fin de prevenir la perdida de una oportunidad para vacunar. Esto ha causado confusión

entre los profesionales de la salud con respecto al momento apropiado de administrar estas vacunas. Un ensayo aleatorizado que evaluó la inmunogenicidad de ZV y PPV23 administrados juntos versus una administración separada de al menos 4 semanas entre cada producto; demostró que los niveles de anticuerpos del virus de la varicela zoster (VZV) del grupo de administración concomitante en comparación con los grupos de vacunación no concomitante, no cumplían con los requisitos de no inferioridad. Sin embargo, un estudio de cohorte, retrospectivo que comparó la incidencia de infecciones HZ tras la administración concomitante de vacunas PPV23 y HZ contra la administración no concomitante; no encontró una diferencia estadísticamente significativa entre los grupos.

CONCLUSIONES: La administración concomitante de ZV y PPV23 es apoyada por el CDC y la FDA para mejorar las tasas de inmunización entre los individuos elegibles a vacunación. Como no hay evidencia directa de que la administración simultánea de ZV y PPV23 pone a los pacientes a mayor riesgo de desarrollar HZ; se les debe proveer las vacunas durante la misma visita de la oficina médica para evitar la pérdida de una oportunidad para vacunar contra 2 enfermedades muy graves.

Traducido por Wilma M Guzmán-Santos

RÉSUMÉ

L'Administration Concomitante du Vaccin 23-Valent Contre le Pneumocoque et du Vaccin Contre l'Herpès Zoster Procure une Protection Adéquate Contre l'Herpès Zoster

MJ Wyman, KL Stabi

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OBJECTIF: Déterminer si l'administration concomitante du vaccin contre le virus de l'herpès zoster (VHZ) et du vaccin polysaccharidique 23-valent contre le pneumocoque (VPP23) procurerait une protection suffisante contre les infections à herpès zoster (HZ).

REVUE DE LA LITTÉRATURE: La littérature révisée a été obtenue via le site web du Centers of Disease Control and Prevention (CDC), PubMed (depuis octobre 2012), et Scopus (depuis octobre 2012) en utilisant ces mots clés: herpès zoster, pneumococcique, vaccin, concomitant, administration simultanée, Pneumovax, Zostavax, et barrières. De plus, les références de chaque publication ont été consultées.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Tous les articles identifiés publiés en langue anglaise ont été évalués. Deux études évaluant l'administration concomitante ou non du VHZ et du VPP23 ont été inclues.

SYNTHÈSE DES DONNÉES: Les données monographiques actuelles recommandent un intervalle de 4 semaines entre l'administration du VHZ et du VPP23, cependant la Food and Drug Administration (FDA), et le CDC encourage l'administration concomitante afin d'éviter de rater l'opportunité de vacciner. Ceci a provoqué de la confusion chez les professionnels de la santé quant au moment approprié d'administration de ces vaccins. Une étude randomisée qui évaluait l'immunogénicité du VHZ et du VPP23 donnés ensemble comparativement à l'administration séparée d'au moins 4 semaines a démontré que les taux d'anticorps contre le virus varicelle-zona (VVZ) du groupe concomitant par rapport au groupe non-concomitant n'ont pas atteint les critères de non-infériorité. Par contre, une vaste étude de cohorte rétrospective qui comparait l'incidence d'infection à HZ suite à l'administration concomitante par rapport à l'administration non-concomitante du VPP23 et du VHZ n'a pas trouvé de différence statistiquement significative entre les 2 groupes.

CONCLUSIONS: L'administration concomitante du VHZ et du VPP23 est préconisée par le CDC et la FDA pour améliorer les taux d'immunisation chez les individus éligibles à la vaccination. Puisqu'il n'y a pas de preuve directe que l'administration simultanée du VHZ et du VPP23 augmente le risque du patient de développer une infection à HZ, ils devraient être administrés lors de la même visite afin d'éviter de rater l'opportunité de vacciner contre deux maladies très graves.

Traduit par Louis Boisvert