Zoster Vaccine in Immunocompromised Patients: Time to Reconsider Current Recommendations

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(See the Major Article by Tseng et al on pages 913–9.)

Keywords. cancer chemotherapy; herpes zoster; immunization; varicella-zoster virus; zoster vaccine.

Reduced cell-mediated immunity (CMI) to varicella zoster virus (VZV) is associated with an increase in the risk and severity of herpes zoster (HZ) and its debilitating complications, including postherpetic neuralgia (PHN). This is true whether the reduction in VZV CMI is due to the age-related decline in CMI observed in normal older adults, or to immunosuppression caused by certain diseases or their treatments. Zoster vaccines containing the Oka strain of live attenuated VZV have proven to be safe and effective in older adults, but current recommendations preclude their use in immunocompromised persons. In this issue of Clinical Infectious Diseases, Tseng et al \(^1\) report that zoster vaccine, administered to adults \(\geq 60\) years of age, continued to protect against HZ when recipients subsequently underwent cancer chemotherapy. These findings underline the importance of administering zoster vaccine to immunocompetent older adults as currently recommended \(^2\), and doing so as early as possible. In addition, the results of these and similar studies suggest that it may be time to review the current policy of excluding all immunocompromised persons from receiving zoster vaccine.

The study by Tseng et al \(^1\) was conducted among members of Kaiser Permanente Southern California (KPSC), an integrated healthcare system that provides prepaid comprehensive healthcare to its 3.6 million community-dwelling members, and tracks demographics, services, and diagnoses in KPSC electronic health records from outpatient, emergency department, and hospital encounters. KPSC provides zoster vaccine to its members, as recommended \(^2\), at no charge. The cohort studied consisted of KPSC members aged \(\geq 60\) years who received cancer chemotherapy with myelosuppressive agents between 1 January 2007 and 31 December 2012. The 30-month cumulative incidence of HZ in 4710 patients who had received zoster vaccine prior to initiation of chemotherapy was 12.87 per 1000 person-years, compared with 22.05 per 1000 person-years in 16 766 comparable patients who did not receive zoster vaccine. The incidence of HZ reported in unvaccinated patients receiving cancer chemotherapy is approximately twice that observed in placebo recipients in the Shingles Prevention Study \(^3\), 1.5 times that reported in patients with rheumatoid arthritis receiving anti–tumor necrosis factor (TNF) biologics \(^4-6\), and similar to that reported in patients with rheumatoid arthritis receiving anti-TNF biologics and corticosteroids \(^6\) and in other immunosuppressed patients, including solid organ transplant recipients \(^4,7,8\). The incidence rate ratio of HZ in the KPSC patients who received zoster vaccine prior to initiation of cancer chemotherapy compared with those who did not was 0.58, corresponding to zoster vaccine effectiveness of 42%.

This study was not able to determine zoster vaccine safety or effectiveness in cancer patients who received zoster vaccine \(\leq 60\) days before beginning chemotherapy because of the small number of patients \((n = 152; 3.2\% of the vaccine recipients) vaccinated during this time interval. As the authors noted, the Advisory Committee on Immunization Practices recommendation to administer zoster vaccine at least 14 and, preferably, 30 days prior to initiating cancer chemotherapy has not been adequately investigated. The study highlights the need for further investigation of the consequences of administering zoster vaccine in accordance with these recommendations, as
the results would have important ramifications for clinical practice. Once the diagnosis of cancer is made, oncologists and patients do not want to delay the initiation of chemotherapy for many cancers beyond 14–30 days. Thus, for many patients who have not already received zoster vaccine, the decision whether or not to administer it must be made relatively quickly. The more information we have regarding safety and efficacy the better.

Langan et al [4] determined incidence rates of HZ and PHN among 766,330 eligible Medicare members aged ≥65 years who received (29,785) or did not receive (736,545) zoster vaccine between 1 January 2006 through 31 December 2009. To increase the specificity of diagnosis, incident cases of HZ were identified by the first HZ diagnostic code occurring during follow-up that was accompanied by a pharmacy claim for antiviral treatment within 7 days before or after. PHN of >90 days’ duration was identified in patients with a first episode of HZ who had a further HZ diagnostic code after 90 days, together with a relevant prescription for an analgesic, anticonvulsant, or antidepressant on the same day. A diagnostic code for non-specific neuralgia or neurologic complications of HZ after 90 days was also indicative of PHN. At some time during the study period, 140,925 individuals were immunosuppressed, including 4469 who were immunosuppressed at the time of zoster vaccine administration. The number of subjects who were immunosuppressed at the time of zoster vaccine administration is similar to the total number of subjects who received zoster vaccine prior to initiation of cancer chemotherapy in the study by Tseng et al. Langan et al demonstrated overall vaccine effectiveness for HZ of 48%, and vaccine effectiveness for PHN of >90 days’ duration of 59%; vaccine effectiveness for HZ in immunosuppressed individuals was 37%.

In the Shingles Prevention Study, vaccine efficacy for HZ in persons aged ≥60 years was 51% and vaccine efficacy for PHN of >90 days’ duration was 67%. Vaccine efficacy for the burden of illness due to HZ pain and discomfort (a measure of the total adverse impact of HZ on an affected individual, which was not assessed in any of the studies discussed here) was 62% [3].

In a retrospective cohort study of Medicare beneficiaries 60 years of age and older, Zhang et al [5] used Medicare claims data from 1 January 2006 through 31 December 2009 to examine the association between vaccination against HZ and the subsequent incidence of HZ in 463,541 patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease, 18,683 (4.0%) of whom received zoster vaccine. Incident cases of HZ were identified by the first HZ diagnostic code occurring during follow-up that was accompanied by a pharmacy claim for antiviral treatment within 7 days before or after. Safety in the first 42 days after administration of zoster vaccine was assessed by identifying episodes of HZ or conditions that might represent complications caused by dissemination of vaccine virus, including diagnostic codes for varicella/chickenpox and hospitalization for meningitis and encephalitis. No safety signals were detected during the first 42 days after vaccination in any vaccine recipient, including 633 who were receiving TNF inhibitors or other biologics. Vaccine effectiveness for HZ was 42% during a median follow-up of 2 years.

Despite its well-documented efficacy against HZ and PHN in older adults, uptake of zoster vaccine is extremely low—only 3.9% of the eligible subjects in the study reported by Langan et al [4] and only 20% nationally as of 2012 [9]. The demonstration that older adult recipients of zoster vaccine are likely to continue to derive benefit from zoster vaccine, even if they subsequently become immunosuppressed by disease or treatment and are therefore no longer eligible to receive zoster vaccine according to current recommendations [2], adds to the rationale for vaccinating all eligible adults ≥60 years of age in a timely manner and, perhaps, for vaccinating some at-risk populations at a younger age.

The capacity of zoster vaccine to protect against HZ and PHN in older adults depends on its ability to elicit an anamnestic immune response to VZV in persons who have already experienced primary VZV infection, that is, varicella (chickenpox) during childhood [10]. Such recall responses are less likely to be inhibited by iatrogenic immunosuppression than primary immune responses. The observational studies by Tseng et al [1] and others [4, 5], as well as a prospective study demonstrating the safety of zoster vaccine and its capacity to increase levels of VZV CM1 in human immunodeficiency virus–infected adults with conserved immune function who are biologically suppressed on antiretroviral therapy [11] (C. A. Benson, personal communication), indicate that VZV-specific immunity is well maintained in the presence of iatrogenic immunosuppression and that live attenuated Oka zoster vaccine is safe and likely effective in several different populations of immunocompromised patients. In view of the very high degree of attenuation of the Oka vaccine strain of VZV [12], these observations suggest that it may be time to reconsider the use of zoster vaccine in selected populations of immunocompromised patients who are at increased risk of HZ infection and its debilitating complications. Such considerations should not, however, divert attention from the urgent need to increase the woefully inadequate uptake of zoster vaccine by adults ≥60 years of age, for whom it is already recommended.

Notes
Acknowledgments. The authors thank Dr Ruth Harbecke for her critical review of the manuscript.

Financial support. M. N. O. is supported, in part, by the James R. and Jesse V. Scott Fund for Shingles Research.
**Potential conflicts of interest.** Both authors: No reported conflicts.
Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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