Editorial

# The Herpes Zoster Vaccine in Rheumatic Diseases: Duration of Response

Shingles is painful. Anyone who has experienced shingles will tell you that in no uncertain terms. By now, we are quite aware of the increased risk of herpes zoster (HZ) in patients with autoimmune diseases due to immunosuppressive medication use or from immune dysregulation from the underlying disease. Unfortunately the very same risks for HZ reactivation are precisely those that raise concern for theoretical risks of contracting vaccine-strain varicella infection from the live-attenuated HZ vaccine (Zostavax, Merck); and this has resulted in undervaccination of many people with rheumatic diseases who would otherwise be eligible for vaccination. Until recombinant varicella vaccines become commercially available, the live-attenuated vaccine is the only protective measure available for our patients.

While it is easy to provide arguments for increased vaccination of patients with rheumatic disease in whom levels of immunosuppression are mild to moderate (with tofacitinib being a notable contraindication[1]), it is also time to focus on the available data for safety, efficacy, and duration of protection provided by the HZ vaccine when given to patients who may have blunted responses because of underlying autoimmune diseases and/or chronic immunosuppressive therapy. We do not have the benefit of the sheer numbers of rheumatic disease subjects to perform a randomized, placebo-controlled clinical trial of HZ vaccination akin to the Shingles Prevention Study (38,546 subjects)[2]. Therefore we must rely on administrative data to examine rates of vaccine exposure and the effects on episodes of HZ reactivation.

Recent analyses have provided a reasonable alternative to analyze HZ reactivation after vaccination in patients with rheumatic disease by analyzing large administrative datasets with a relatively large number of individuals with autoimmune disease who have received the currently available HZ vaccine. This is exceptionally helpful because such patients were excluded from the large Shingles Prevention Study and other randomized controlled trials for HZ vaccination. Initial reports found a very low level of vaccination among patients > 50 years old with inflammatory arthritides (1.2%) in the first years after vaccine licensure (2006); however, vaccination rates remained low, even for patients not receiving immunosuppressive medications[3]. A followup study was done to identify the risk of developing HZ within 42 days of vaccination (potentially vaccine strain-related infection) and to evaluate the role of background immunosuppressive medications (biologic or disease-modifying drugs) on immediate postvaccination HZ[4]. Rates of HZ within 42 days of vaccination were not increased above rates of HZ in the unvaccinated population of subjects with inflammatory diseases. The study identified more than 600 subjects who received the HZ vaccine while taking background biologic therapies: none developed HZ within 42 days. Further, rates of HZ were lower in vaccinated (10,868 person/yrs of exposure) compared to unvaccinated individuals (854,609 person/yrs) over the subsequent 2 years. The limitations of the study were the inability to verify diagnoses, potential misclassification of individuals who held their biologic medication in anticipation of HZ vaccination, and restriction of the population to Medicare beneficiaries. However, in the absence of other available data, this study provides some reassurance about the relative safety of the vaccine as well as some preliminary evidence of effectiveness. In fact, this study demonstrated a nearly 40% reduction in risk of HZ among vaccinated individuals. Although not as high as that seen in immunocompetent populations (51% risk reduction), vaccination still offers a significant level of protection.

The study by Yun, *et al* in this issue of *The Journal* addresses the next question related to HZ vaccination in individuals with rheumatic diseases — the duration of response[5]. Duration of response is a necessary consideration when determining cost-effectiveness of vaccination as well as whether and when booster vaccinations would be warranted. The original Shingles Prevention Study demonstrated that vaccine efficacy persisted for at least 4 years following exposures; longterm extension studies of the original immunocompetent population found that protection waned to near zero after 8 to 10 years[6]. Studies analyzing the effectiveness of booster HZ vaccination have not yet

*See* Herpes zoster vaccine in autoimmune and inflammatory diseases, *page 1083*





*The Journal of Rheumatology 2017; 44:7; doi:10.3899/jrheum.170321*

been performed systematically in immunocompetent or other populations.

The current study[5] evaluated nearly 60,000 vaccinated patients and compared rates of HZ with a matched cohort of nearly 120,000 unvaccinated patients with rheumatic disease. In addition to the large number of patients studied, the authors were able to control for use of biologic, traditional disease-modifying agents and corticosteroid use as they compared HZ rates over a mean of 7 years postvaccination. Consistent with what we would expect in individuals with autoimmune diseases, the duration of response seen in this study appears to be somewhat blunted, but was found to last about 5 years. Thus, despite the diminished responses when compared to immunocompetent individuals, patients with rheumatic diseases do make meaningful and effective responses to HZ vaccine that last for several years.

Although we should remain cautious about the potential risk for inducing vaccine-strain illness in our patients, we have evidence that the current HZ vaccine does work in patients with rheumatic disease, who are, by way of disease-related immune dysfunction as well as immunosuppressive medication use, already at increased risk of developing HZ. Vaccination rates remain very low in patients with rheumatic disease, even for those who are not taking biologic therapies and who meet criteria for vaccination. Strategies need to be developed to enhance vaccination rates for HZ in rheumatic diseases aged 50 years and older. Additionally, use of this vaccine in younger adults with underlying autoimmune diseases should be considered and studied to reduce the burden of HZ disease in younger adults who remain at increased risk[7].

**ERIN SHIRLEY,** BS;
**ELIZA F. CHAKRAVARTY,** MD,
Associate Member,
Arthritis and Clinical Immunology,
Oklahoma Medical Research Foundation,
Oklahoma City, Oklahoma, USA.
Address correspondence to Dr. E.F. Chakravarty, Associate Member, Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, 825 NE 13th St., Oklahoma City, Oklahoma 73104, USA.
E-mail: chakravartye@omrf.org

## REFERENCES

1. Yamaoka K. Benefit and risk of tofacitinib in the treatment of rheumatoid arthritis: a focus on herpes zoster. Drug Saf 2016;39:823-40.
2. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:3371-84.
3. Zhang J, Delzell E, Xie F, Baddley JW, Spettel C, McMahan RM, et al. The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study. Arthritis Res Ther 2011;13:R174.
4. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA 2012;308:43-9.
5. Yun H, Xie F, Baddley JW, Winthrop K, Saag KG, Curtis JR. Longterm effectiveness of herpes zoster vaccine among patients with autoimmune and inflammatory diseases. J Rheumatol 2017;44:1083-7.
6. Morrison VA, Johnson GR, Schmader KE, Levin MJ, Zhang JH, Looney DJ, et al. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis 2015;60:900-9.
7. Yun H, Yang S, Chen L, Xie F, Winthrop K, Baddley JW, et al. Risk of herpes zoster in autoimmune and inflammatory diseases: implications for vaccination. Arthritis Rheumatol 2016;68:2328-37.

J Rheumatol 2017;44:968–9; doi:10.3899/jrheum.170321