Risk of Disseminated Disease in Immunosuppressed Patients Receiving Live Zoster Vaccine

To the Editor: I read with interest the letter by Bubb[1] and the reply by Cheetham et al[2] in the November 2015 issue of *Mayo Clinic Proceedings* regarding the risk of disseminated disease in immunosuppressed patients receiving live zoster vaccine. Although the vaccine has been found to be highly effective and there is a paucity of cases of vaccine-related infections, the following report serves to highlight the need for caution when immunizing highly immunosuppressed patients.

A 62-year-old man who had granulomatosis with polyangiitis (Wegener granulomatosis) diagnosed 5 years previously was admitted to the Michael E. DeBakey VA Medical Center in February 2015 with a rash that began on his face 2 days before admission and had spread to his trunk, upper arms, and legs. In 2014, he had been admitted to another hospital with pulmonary hemorrhage and was treated with rituximab, methylprednisolone, and azathioprine. The patient had schizophrenia and nonischemic cardiomyopathy with an ejection fraction of 30%. At the time of admission, he was taking prednisone, 40 mg/d orally, plus mycophenolate mofetil, 500 mg orally twice daily. He also was undergoing hemodialysis thrice weekly. He had accidentally received a subcutaneous injection of Zostavax, 0.65 mL (live varicella vaccine), at a VA outpatient clinic 47 days before admission.

In the emergency department of the DeBakey Medical Center, the patient was short of breath and was noted to have cushingoid features (moon facies, lipodystrophy, and central obesity). There were hemorrhagic monotonous vesicles on an erythematous base covering the trunk, the proximal and distal upper extremities, and the proximal lower extremities. A punch skin biopsy revealed immunohistochemical evidence of human herpesvirus 3. The tissue block was later sent to the Centers for Disease Control and Prevention's Herpesvirus Laboratory, where the virus was confirmed to be the vaccine strain. The patient experienced respiratory distress and required emergent tracheal intubation and mechanical ventilation. Chest radiography revealed bilateral lung infiltrates, and both sputum and blood cultures grew methicillin-resistant *Staphylococus aureus*. Bronchoscopy revealed purulent secretions but no evidence of pulmonary hemorrhage. Treatment included acyclovir, vancomycin, and cefapime. Although the bacteremia cleared and there was crusting of some of the skin lesions, the patient's condition gradually worsened, and eventually the family requested that treatment be discontinued; the patient died after 2 weeks of hospitalization. The event was investigated, and the guidelines for varicella zoster virus vaccination within the clinics were reviewed with all staff to ensure that such an event does not recur.

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1. Bubb MR. Risk of disseminated varicella zoster in immunosuppressed patients receiving zoster vaccination. *Mayo Clin Proc.* 2015;90(11):1585-1586.
2. Cheetham TC, Sy LS, Jacobsen SJ. In reply—Risk of disseminated varicella zoster in immunosuppressed patients receiving zoster vaccination. *Mayo Clin Proc.* 2015;90(11):1586-1587.

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In Reply I—Risk of Disseminated Disease in Immunosuppressed Patients Receiving Live Zoster Vaccine

The package insert for Zostavax lists "immunosuppression or immunodeficiency" as contraindications for use, so complications resulting from its use in a very highly immunosuppressed patient may be anticipated.[1] However, reports of such complications, such as those described by Dr Young, remain rare. The risks of Zostavax become notable somewhere between moderate and very high levels of immunosuppression, and data, such as results from the ongoing VERVE trial[2] of vaccination during treatment with anti—tumor necrosis factor therapy, are needed to define risks in specific populations. In the case described by Dr Young, dissemination occurred 45 days after vaccination, whereas current trials of Zostavax vaccination during immunosuppression have a shorter window for evaluation of vaccine safety.

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1. Zostavax [package insert]. Whitehouse Station, NJ: Merk & Co, Inc; 2006, 2014.
2. A Pilot Study of the Safety and Effectiveness of the Live Zoster Vaccine in Anti-TNF Users. ClinicalTrials.gov Identifier NCT01967316.

http://dx.doi.org/10.1016/j.mayocp.2016.04.016

In Reply II—Risk of Disseminated Disease in Immunocompromised Patients Receiving Live Zoster Vaccine

The case reported by Dr Young illustrates the potential for vaccine-related herpes zoster infections in highly immunosuppressed patients. In our original study published in the July 2015 issue of *Mayo Clinic Proceedings*,[1] there were only 500 individuals who were receiving corticosteroid doses similar to the regimen reported in this case, and

therefore, conclusions could not be drawn regarding the safety of the zoster vaccine in the population we described. The case reported by Dr Young highlights the need for caution or possibly withholding zoster vaccination in highly immunosuppressed patients.

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1. Cheetham TC, Marcy SM, Tseng HF, et al. Risk of herpes zoster and disseminated varicella zoster in patients taking immunosuppressant drugs at the time of zoster vaccination. *Mayo Clin Proc*. 2015;90(7):865-873.

http://dx.doi.org/10.1016/j.mayocp.2016.04.014

The Different Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Mortality

To the Editor: The article by Bangalore et al[1] published in the January 2016 issue of *Mayo Clinic Proceedings* deals with the important topic of cardiovascular protection. In this regard, several recent studies have compared the 2 classes of cardioprotective drugs, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). As highlighted by Bangalore et al, these studies have often reported mortality reduction with ACE inhibitors vs placebo or comparators, while ARBs were not associated with significant effect.

In this new meta-analysis[1] of trials that included patients with diseases ranging from hypertension to myocardial infarction or diabetes, but excluding heart failure, the authors confirmed that ACE inhibitors significantly lower mortality whereas placebo and ARBs do not. Moreover, the authors provided a hypothesis for this difference: ACE inhibitors were discovered and studied in large randomized trials earlier than ARBs. According to them, in view of the improvement in standard of care over the years, concomitant use of lifesaving drugs such as antiplatelet agents or statins was more likely in patients enrolled in ARB trials. This difference could have contributed to the lower impact of ARBs on mortality. To support this hypothesis, the authors suggested that the rate of mortality and morbidity were higher in the placebo groups of ACE inhibitor trials compared with the placebo groups of ARB trials.

This proposal, however, is not supported by the rate of events in Tables 1 and 2 in their article. Indeed, ACE inhibitor trials lasted on average 3.2 years and ARB trials 3 years. The trials included in their analysis provided a follow-up of roughly 99,836 patient-years for ACE inhibitors and 99,423 patient-years for ARBs. The rate of death was therefore 0.0243 events per patient-year in the placebo arms of ACE inhibitor trials and 0.0299 events per patient-year in the placebo arms of ARB trials. As a consequence, and in contrast with the authors' hypothesis, the rate of death tended to be higher in the placebo groups of ARB trials compared with ACE inhibitor trials.

In addition, my colleagues and I observed in a meta-analysis of studies in patients with hypertension performed since 2000 that ACE inhibitor use was again significantly associated with reduced all-cause mortality by 10% vs the comparator, whereas the ARBs had no such association.[2,3] Savarese et al[4] similarly reported a reduction in mortality with ACE inhibitors vs placebo (−9%; P=.008), while no significant effect was detected with ARBs. Contrary to the assumption of Bangalore et al, in trials considered in the meta-analysis by Savarese et al, the coprescription of statins or aspirin was higher in the ACE inhibitor trials compared with ARB trials (51% vs 33% for statins and 85% vs 27% for aspirin). Therefore, the different effects of ACE inhibitors and ARBs cannot be due to different coadministration of lifesaving agents.

In conclusion, it is possible to compare ACE inhibitors and ARBs in a balanced way, at least when restricting the analysis to contemporary trials in patients with hypertension, and in this context, ACE inhibitors are the only class to show a significant reduction of mortality.

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Potential Competing Interests: The author reports receiving honorarium for consultancy from several pharma developing ACE inhibitors or ARBs, including Daiichi Sankyo, Menarini, BMS, Servier, Bayer.

1. Bangalore S, Fakheri R, Toklu B, Ogedegbe G, Weintraub H, Messerli FH. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? insights from 254, 301 patients from randomized trials. *Mayo Clin Proc*. 2016;91(1):51-60.
2. van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. *Eur Heart J*. 2012;33(16):2088-2097.
3. Brugts JJ, van Vark L, Akkerhuis M, et al. Impact of renin-angiotensin system inhibitors on mortality and major cardiovascular endpoints in hypertension: a number-needed-to-treat analysis. *Int J Cardiol*. 2015;181:425-429.
4. Savarese G, Costanzo P, Cleland JG, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol*. 2013;61(2):131-142.

http://dx.doi.org/10.1016/j.mayocp.2016.04.021

In Reply—The Different Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Mortality

Dr Mourad contends that the angiotensin-converting enzyme inhibitors (ACEis) are the only drug class to produce a major reduction in