Inflammatory chronic diseases: Preventable by vaccines?

Sara L. Worzella and Mary S. Hayney

The body protects from infectious diseases and harmful environmental stimuli by mounting inflammatory responses. However, an overactive inflammatory response can be dangerous. This response is frequently the cause of tissue damage and death.

Specifically, infection can be a contributing factor to atherosclerosis, where the artery wall thickens through the formation of plaques. Atherosclerosis, the leading cause of morbidity and mortality in the Western world, can manifest as peripheral vascular disease, coronary heart disease, and stroke.[1] Recent studies have helped decipher the connections between infectious diseases such as herpes zoster, invasive pneumococcal disease, and influenza, and potentially harmful inflammatory and cardiovascular effects.

There are several proposed mechanisms for how infections contribute to inflammation. Recent studies have prompted further discussion on possible benefits of vaccinations beyond preventing their target illnesses.

Herpes zoster may increase stroke risk

Primary infection with the varicella-zoster virus (VZV) is the cause of chickenpox. The virus remains in a lifelong latent stage in the cranial nerve, dorsal root, and autonomic ganglia.[2] However, spontaneous reactivation of the virus can occur, known as herpes zoster or shingles. This reactivation occurs more frequently with advancing age or in immunocompromised people, when VZV-specific cell-mediated immunity declines.[2] One million cases of herpes zoster are diagnosed each year in the United States,[3] and complications occur in nearly 50% of older persons who develop zoster.[4] Some of these complications include VZV vasculopathy and stroke. One proposed mechanism is direct infection of the cerebral arteries, which can lead to both inflammatory and noninflammatory changes.[5] These vascular changes may accelerate the atherosclerosis process and manifest as ischemic stroke.[2,5]

Three separate studies demonstrated a similar finding: The risk of stroke increases after a herpes zoster attack.

In a study by Lin and colleagues,[2] the risk of stroke following a diagnosis of herpes zoster ophthalmicus was investigated in a retrospective cohort study among adults older than 18 years in the Taiwan National Health Insurance Research Database. The cohort studied was matched by gender and age with a comparison group. Patients with herpes zoster ophthalmicus were found to have a 4.52-fold higher risk of stroke development within 1 year versus the comparison cohort.

Another nationwide cohort study examined Danish adults over 18 years over a span of 12 years who had taken acyclovir for herpes zoster. Sreenivasan and colleagues[6] found an incidence rate ratio of stroke of 1.21 (95% CI 1.14–1.29) within 1 year after herpes zoster. Specifically, a more pronounced risk of 2.27 (95% CI 1.83–2.82) during the first 14 days followed zoster onset, and this risk remained elevated for more than 3 months.

A recent retrospective cohort study in the United Kingdom examined herpes zoster as a risk factor in adults over 18 years of age for vascular diseases including stroke, transient ischemic attack (TIA), and myocardial infarction (MI). Breuer and colleagues[7] found herpes zoster to be an independent risk factor in patients younger than 40 years for stroke, TIA, and MI, with hazard ratios of 1.74 (95% CI 1.13–2.66), 2.42 (95% CI 1.34–4.36), and 1.49 (95% CI 1.04–2.15), respectively.

A vaccine for herpes zoster is currently licensed for persons aged 50 years and older. This vaccine has been shown to increase cell-mediated immunity to VZV in immunocompetent older adults.[8] Although no evidence shows that the zoster vaccine decreases the risk of stroke, a rational individual would conclude that zoster vaccine decreases the risk of zoster and zoster increases the risk of stroke. Prevention of zoster may help prevent stroke.

Pneumococcal vaccination produces anti-oxLDL antibodies

Pneumococcal disease can cause pneumonia, meningitis, or a blood infection.[9] Despite intensive care, pneumococcal disease causes death in one-third of people who contract it. This disease can affect people of all ages. It is the most serious in the very young, persons older than 65 years, and those with other medical issues such as congestive heart failure and diabetes.[9]

A major risk factor for developing atherosclerosis is high serum cholesterol levels.[1] Oxidized low-density lipoprotein (oxLDL) accumulates in atherosclerotic plaques and is a large fraction of the choles-

Send your immunization questions to the *JAPhA* Contributing Editors who coordinate the **Vaccine Update** column:

- Mary S. Hayney, PharmD, BCPS, Associate Professor of Pharmacy, School of Pharmacy, University of Wisconsin, Madison (mshayney@pharmacy.wisc.edu).
- John D. Grabenstein, PhD, Director of Scientific Affairs, Merck Vaccine Division (john_grabenstein@merck.com)

terol present. Antibodies to oxLDL (anti-oxLDL) have been inversely associated with atherosclerotic burden in mouse models.[10] The anti-oxLDL antibodies reduced atherosclerotic plaque in mice.[11] This association also exists in humans but has been more variable due to limited clinical studies.[1]

In a study by Suthers and colleagues,[1] the associations among pneumococcal vaccination, antipneumococcal antibody levels, and oxLDL antibody levels were assessed in a population with no history of cardiovascular disease. The authors found a correlation between antipneumococcal antibodies and anti-oxLDL antibodies. Pneumococcal vaccination was found to induce the production of these antibodies. The production of these antibodies could have a potential protective effect in humans.

However, recent studies have had conflicting results on the cardiovascular protective effects of the pneumococcal vaccine. In a prospective cohort study that examined Spanish adults, pneumococcal vaccination did not alter the risk of ischemic stroke over a time horizon of 3 years.[12] Due to limited data, a larger prospective clinical trial is required to further investigate the association between these anti-oxLDL antibodies in vaccinated patients and a potential protective effect.

Vaccines are available that contain pneumococcal serotypes most likely to cause invasive disease. Pneumococcal conjugate vaccine, 13 valent (Prevnar 13—Pfizer) is recommended for children younger than 5 years and children and adults 19 years or older with certain immunosuppressing conditions. Pneumococcal polysaccharide vaccine, 23 valent (Pneumovax 23, Merck Vaccines) is recommended for all adults older than 65 years and for persons 2 years or older who are at high risk for invasive disease, including adults aged 19 through 64 who smoke cigarettes or have asthma.

Influenza vaccination may reduce cardiovascular risk

Influenza is a highly contagious respiratory illness caused by influenza viruses that infect the nose, throat, and lungs. Approximately 5% to 20% of the population in the United States contract influenza each year.[13]

Numerous studies have compiled evidence showing an association between influenza infection and a higher incidence of cardiovascular events.[14] More specifically, spikes have occurred in the rates of hospitalization for acute myocardial infarction and mortality during influenza seasons.[13] Several different hypothesized mechanisms explain how the influenza virus promotes inflammation. Udell and colleagues,[15] through an analysis of four studies, showed that influenza vaccination reduced the risk of cardiovascular events by 48% in the following year.

More recently, a case–control study of individuals hospitalized in Australia found that the risk of acute myocardial infarction (AMI) was reduced by 45% with influenza vaccination.[16] In this case, the influenza vaccination may have served as a protective factor or acted through another mechanism in the immune system. A similar case–control study found a 25% reduction in stroke risk with vaccination.[17]

Larger clinical trials will be necessary to further explore the mechanism of influenza vaccination in this association. However, even in the absence of an elucidated mechanism, the American College of Cardiology and the American Heart Association recommend annual influenza vaccine for patients with heart disease at the same level of evidence as controlling blood pressure and lowering cholesterol.[18]

Influenza vaccines vary in effectiveness year to year based, in part, on their degree of matching three influenza virus subtypes predicted to circulate in the coming year. Annual influenza vaccine is recommended for all individuals older than 6 months.

Pharmacist's role

Vaccines annually prevent 6 million deaths worldwide.[19] When analyzing the impact of immunization, the focus is often and appropriately placed on the prevention of the primary infectious diseases. The studies discussed above demonstrate how infectious diseases may also be closely related to associated diseases such as stroke and cardiovascular disease. These secondary effects can have a greater long-term burden, both medically and economically, than the acute course of infectious disease.

Pharmacists are in a vital position to provide this education to patients and other health care professionals. By promoting immunization and helping to decrease barriers, pharmacists may be reducing these burdens on an even larger scale.

Sara L. Worzella, BS, MS
Student Pharmacist
School of Pharmacy
University of Wisconsin
Madison

Mary S. Hayney, PharmD, MPH, BCPS
Associate Professor of Pharmacy
School of Pharmacy
University of Wisconsin
Madison
mshayney@pharmacy.wisc.edu

doi: 10.1331/JAPhA.2014.14526

References

1. Suthers B, Hansbro P, Thambar S, et al. Pneumococcal vaccination may induce anti-oxidized low-density lipoprotein antibodies that have potentially protective effects against cardiovascular disease. Vaccine. 2012;30:3983–3985.
2. Lin HC, Chien CW, Ho JD. Herpes zoster ophthalmic and the risk of stroke: a population-based follow-up study. Neurology. 2010;74(10):792–797.
3. Tseng HF, Smith N, Harpaz R, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. JAMA. 2011;305(2):160–166.