

Influenza Vaccination of Patients Receiving Statins: Where Do We Go From Here?

Robert L. Atmar^{1,2} and Wendy A. Keitel^{1,2}

¹Department of Medicine and ²Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas

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Atherosclerotic vascular disease is a leading cause of morbidity and mortality in the United States [1]. Cardiovascular events also are a major contributor to excess mortality seen during influenza epidemics [2]. Statins were developed to treat hypercholesterolemia, and their use as primary or secondary prevention of atherosclerotic vascular disease has significantly reduced all-cause mortality and major vascular events in at-risk populations [3]. Their impact on human health has led to their use in >40% of the US population aged >65 years [4]. Statins also have immunomodulatory effects [5], and it has been suggested that their use may have protective effects during an influenza pandemic [6]. A decreased risk of mortality has been reported in persons with laboratory-confirmed acute influenza receiving a statin medication concomitantly [7], although this observation may have been explained by a healthy-user bias due to inadequate control for health-related differences among persons receiving and those not receiving a statin [8, 9]. Other studies have failed to find a benefit

among influenza virus-infected persons taking a statin, compared with those not receiving such therapy [9, 10]. From these results, whether statin use has a favorable impact on influenza-related disease remains unresolved.

Vaccination is currently the primary method for preventing influenza-related illness and complications [11]. Could statin use have an adverse effect on vaccine immunogenicity and resulting vaccine effectiveness (VE), based upon its immunomodulatory effects? Two new studies reported in the current issue of *The Journal of Infectious Diseases* explore these questions.

Black et al [12] performed a post hoc analysis of a randomized controlled trial originally conducted to evaluate the effect of an adjuvant, MF59, on the immunogenicity of trivalent inactivated influenza vaccine (IIV3) in persons aged >65 years. In the current report, they examined the effect of statin use on vaccine-induced immune responses. Statin users had significantly reduced serum hemagglutination-inhibition (HAI) antibody responses, compared with non-statin users, and the effect was most marked in those using synthetic statins, compared with those using fermentation-derived statins. Not surprisingly, there were significant differences between the 2 populations, with a greater frequency of statin users having underlying diseases. In addition, the prevalence of statin use (19.8%) in the study population was much lower than expected

for a US population aged >65 years, likely reflecting a lower frequency of statin use among persons enrolled from other countries. The authors tried to control for these differences by including variables associated with vaccine response (age, sex, prevaccination HAI titer, and high-risk status). Receipt of IIV in the prior year is another variable that can affect vaccine response adversely [13], and it is probable that statin users would have been more likely to receive IIV in the previous year. Persons enrolled from non-US countries may also have been less likely to receive IIV in the prior year. To address the differences in statin use and IIV uptake, the authors analyzed responses among seronegative persons in the United States, reasoning that these persons would have been less likely to be vaccinated in the previous year. Significantly lower antibody responses to 2 of 3 vaccine antigens were still present among statin users.

Omer et al [14] performed a retrospective study to determine the impact of statin use on influenza VE, calculated with information captured in a database from a large managed care organization in Georgia. The investigators identified medically attended acute respiratory illness (MAARI), as well as influenza vaccination status and statin use, among adults in the managed care organization during each of 9 influenza seasons between 2002 and 2011. MAARI is a commonly used indicator of the impact of influenza in a population [15], although it can be caused

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Correspondence: Robert L. Atmar, MD, Baylor College of Medicine, One Baylor Plaza, MS BCM280, Houston, TX 77030 (ratmar@bcm.edu).

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by more than just influenza virus infection and can occur when influenza virus is not circulating. They computed incidence rates of MAARI for patients who did and those who did not receive influenza vaccine during 3 periods: when influenza was widespread, circulating throughout the state; when influenza transmission was only occurring locally; and when there was no influenza circulation. The investigators then calculated incidence risk ratios (IRRs) by dividing the incidence rate for vaccine recipients by that for unvaccinated persons. The IRR of MAARI was >1 during all 3 periods, indicating a higher MAARI rate among vaccine recipients, compared with unvaccinated persons. The same was true for those receiving a statin. As has been seen in other database analyses of other influenza-related outcomes [16], the frequency of MAARI when no influenza is circulating was higher among vaccine recipients than among non-vaccine recipients, reflecting a healthy-user bias. Patients who receive IIV are more likely to access medical care when ill than those who are not vaccinated. To address this problem, the investigators calculated a relative risk ratio, using the IRR during the period when no influenza was circulating to adjust the IRRs observed when influenza circulation was local or widespread, expressing the result as a relative risk ratio. With this adjustment and adjustment for selected other factors (age, certain underlying diseases, receipt of pneumococcal vaccine, and well-person visits during the influenza season), vaccinated patients were significantly less likely to present with MAARI when influenza circulation was local or widespread. This method also was used to evaluate the influence of statin use on VE. Persons not using statins had a significantly higher VE than those receiving statins, when influenza circulation was widespread, suggesting that statins adversely affected VE. As in the study by Black et al, the patient population taking statins was significantly different from the population of nonusers, and data on influenza vaccine

use in the prior year were not included in the analysis.

Despite the potential limitations from unrecognized biases and confounders inherent in the designs of these two studies, the findings that statin use adversely affects IIV immunogenicity and VE are biologically plausible, based on known immunomodulatory effects of these drugs, and raise important questions about the use of these important medications. Should these results affect a physician's care of patients? Should statins be stopped for a period while influenza vaccine is administered? Should IIV not be administered to statin users? In our opinion, the answer to all of these questions is no. Instead, the results of these studies should be viewed as hypothesis generating and should prompt further investigations into whether statins reduce IIV immunogenicity and, if so, the mechanisms by which immune responses and associated VE are adversely affected. A major challenge is to select study designs that reduce the potential for confounding, as randomized trials of IIV are no longer considered ethical in many countries. In terms of immunogenicity, it might be possible to randomly assign statin candidates to receive therapy immediately or after a delay, with the goal of assessing the effect of statins on immune responses after influenza vaccination. If statins are found to reduce immunogenicity, then potentially transient interruption of statin therapy could be considered for testing. The effect of chronic statin use on the immunogenicity of other vaccines also needs to be evaluated further. With regard to VE, studies assessing statin use and influenza vaccination among patients who are positive versus those who are negative for influenza virus presenting with MAARI are likely to provide better estimates of VE with less chance of confounding bias [17]. Differences between synthetic statins and those produced using fermentation are intriguing. One possible explanation for this effect might be the greater inhibition of HMG-CoA reductase by synthetic statins, leading to disruption of the

isoprenylation of several intracellular signaling proteins that act as molecular switches [18]. Future studies could also evaluate whether alternative vaccination strategies associated with improved immunogenicity, such as high-dose [19], intradermally delivered [20], or adjuvanted vaccines [12, 21], will overcome the adverse effects of statin use (if any). In the end, risks and benefits of both interventions will need to be weighed and alternative strategies developed to mitigate adverse drug interactions.

These studies also highlight the numerous factors that must be considered when assessing influenza vaccine immunogenicity and VE. These include age [22], sex [23], receipt of influenza vaccine in the prior year [13], presence of an immunocompromised condition [24], presence of other underlying diseases [25], and frailty [26]. The results also underscore the need for the development of influenza vaccines with improved efficacy and effectiveness.

Note

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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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