Statins and Influenza: Can We Move Forward?

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(See the article by Vandermeer et al, on pages 13–19.)

Currently, the 2 main strategies for control of influenza are immunization and antiviral drugs. However, despite increasing uptake of influenza vaccine among the highest risk groups—namely, the elderly and persons with underlying cardiopulmonary diseases—morbidity and mortality from influenza continues to rise in the United States [1]. This paradox has stimulated a heated debate regarding the true efficacy of influenza vaccination in older persons [2, 3]. Some investigators suggest efficacy may be negligible in this group, and even the most optimistic proponents of immunization concede that the current licensed standard dose of inactivated vaccine is less immunogenic and protective in older persons than in young healthy persons [4, 5, 6]. Antiviral therapy, principally with neuraminidase inhibitors, has been shown repeatedly in placebo-controlled trials to be effective when administered to both young and old outpatients early in the course of illness [7, 8]. Although controlled studies in inpatients are strikingly absent, one observational analysis from Toronto noted a 79% reduction in mortality in patients treated with a neuraminidase inhibitor, even when administered after the 48-hour window following symptom onset [9]. Despite availability of vaccine and antivirals, additional therapeutic measures for influenza would be welcomed.

In this issue of the *Journal*, Vandermeer and collaborators report that statin use is associated with reduced mortality during and after hospitalization with influenza infection [10]. The investigators analyzed 30-day mortality in 3043 patients hospitalized with influenza in 10 states as part of the Centers for Disease Control and Prevention's Emerging Infections Program. After adjusting for other variables, such as age, underlying medical conditions, and influenza vaccination, they reported a striking 41% reduction in mortality (odds ratio, 0.59 [95% confidence interval, .38–.92]) in persons on statins either prior to or during hospitalization.

Although not the first study to note such an effect, this article adds significantly to the slowly accumulating evidence that statins may reduce the substantial annual morbidity and mortality from influenza [11–15]. The analysis and results are similar to 2 other published retrospective observational studies that also noted reduced mortality from influenza or pneumonia in persons receiving statins [13, 14]. However, in neither of the previous studies could mortality be specifically linked to a laboratory-confirmed influenza illness, and thus their results suggest a broad effect of statins on all causes of pneumonia mortality rather than specifically on influenza mortality. One of the important strengths of the current study is that only patients with laboratory-confirmed influenza were included in the analysis, thus avoiding the uncertainty of disease misclassification associated with *International Classification of Diseases, Tenth Revision* coding of influenza or pneumonia cases. It also circumvents the possible variable effects of statins on illness due to a variety of pathogens, each with potentially different pathogenic mechanisms. It should also be noted that a recent analysis of documented 2009/H1N1 pandemic influenza cases from the United Kingdom found a similar trend toward reduced mortality related to statin use, although results did not reach statistical significance possibly due to the much smaller number of subjects analyzed [15]. Interestingly, the authors of that article calculated that statistical significance would have required approximately 3000 cases, the same number analyzed in the Vandermeer study.

Like all observational studies, however, the results and conclusions by the Centers for Disease Control and Prevention investigators and their colleagues may be affected by unrecognized factors. The most widely implicated factor is what is commonly referred to as the "healthy user" bias, in which persons on statins are more apt to be more discriminating users of healthcare in general and to lead healthier lifestyles that could affect mortality [16]. Ironically, similar concerns are also at the heart of the debate regarding the reported efficacy of

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influenza vaccine in the elderly from analyses of uncontrolled observational databases [1, 17]. Not surprisingly, in the current analysis statin users were 50% more likely to have received an influenza vaccine than nonusers, perhaps because of a higher incidence of high-risk conditions but also because they were healthy users. It should also be noted that neither influenza vaccine nor antiviral therapy was associated with reduced mortality, although the point prevalence of the latter demonstrated a nonsignificant trend toward benefit (odds ratio, 0.79).

The biological plausibility of a beneficial effect of statins on influenza is well established. Not long after their introduction for treatment of hypercholesterolemia, the pleiotropic anti-inflammatory properties of statins were established, followed more slowly by the appreciation that patients on statins seemed to fare better with sepsis, acute lung injury, and community-acquired pneumonia [18, 19]. Like many other infections, the clinical severity of influenza likely reflects the sum of damage caused by the pathogen itself and the host's inflammatory immune response [20, 21]. Influenza is directly cytotoxic to tracheal epithelial cells, predisposing to bacterial adherence and invasion of the lower airway. However, host innate and adaptive immune responses, characterized by elevated local and systemic proinflammatory cytokines and an influx of polymorphonuclear neutrophils and lymphocytes, are thought to be of equal or greater importance in disease pathogenesis. Statins inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, the key enzyme in the mevalonate pathway leading to the production of cholesterol [22]. This pathway also alters cell membrane signaling transduction, thereby affecting a number of immune mechanisms, including effects on B and T cells, regulatory T cells, dendritic cells, vascular endothelial cell function, and clotting. Statins are potent inhibitors of cytokine synthesis and can downregulate expression of major histocompatibility complex class II, but not class I, antigen complexes. It is likely through these interrelated effects that statins modulate the inflammatory response during influenza infection.

The study by Vandermeer et al [10] raises several important questions about the relationship between statins and influenza mortality. What is the mechanism by which statins reduce mortality? Influenza epidemics are associated with increases in bacterial pneumonia, and infection with *Streptococcus pneumoniae* and *Staphyloccocus aureus* are well-recognized and lethal complications of influenza [23]. Several observational studies have indicated that addition of a macrolide to β-lactam antimicrobials for pneumococcal pneumonia results in improved outcomes, presumably as a result of their anti-inflammatory properties rather than an antibiotic effect [24]. It is unlikely that statin users were more likely to receive a macrolide than nonusers, but it is possible that statins may be most effective in influenza complicated by bacterial infection. Alternatively, the beneficial effect of statins may be due to their anti-inflammatory effect on atherosclerotic vascular endothelium and/or effects on clotting, thereby reducing the incidence of fatal heart attacks and strokes associated with influenza epidemics [25, 26, 27]. Since the cause of death was not reported by Vandermeer et al, nor likely to be uncovered by chart reviews since many deaths occurred outside of the hospital, we can only speculate about the mechanisms at play. Another unanswered yet very important question is whether the timing or duration of statin use in relation to influenza infection is important. Is the benefit only noted when statins are taken prior to infection, or are they equally effective if begun after symptom onset? Since most subjects, if not virtually all, were taking statins prior to admission, this issue could not be addressed. Perhaps additional results from animal models can be helpful in this regard.

So where do we go from here? First, additional high-quality prospective observational studies of laboratory confirmed influenza could be carried out in order to confirm the findings noted by Vandermeer et al. For several years some authorities have suggested that statins might be a viable therapeutic option for influenza [28–31]. It has been argued that this may be a particularly useful approach during pandemics when vaccines might not be available or should antiviral drug resistance be prevalent. It seems highly unlikely, however, that a prospective randomized trial of long-term statin administration prior to influenza infection would be done, not only because of the logistic problems of a large multicenter study but also because it is improbable that clinicians would administer statins solely for the purpose of reducing the severity of influenza. Confirmatory results from additional observational studies would, however, lend support to such a strategy in the event of another pandemic, as has been suggested previously by Fedson [28].

The more obvious study is a double-blind, placebo-controlled, randomized trial of acute statin therapy in hospitalized statin-naive, influenza-infected persons. A similar trial in patients admitted to intensive care with influenza respiratory failure has been proposed by a Canadian consortium [32]. Such a study might be difficult to perform in the United States because a high percentage of older persons are already receiving long-term statin therapy, and it is precisely these patients who may benefit most from acute statin therapy during influenza virus infection. Without a definitive randomized study to assess acute statin use in influenza, the potential benefit will remain debatable and open to the same criticisms regarding the value of influenza vaccines in the elderly and the value of antiviral therapy in hospitalized persons. Hopefully such a fate can be avoided, and we can soon learn if we have a useful new adjunctive treatment for influenza.

Notes

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