

# Influence of Statins on Influenza Vaccine Response in Elderly Individuals

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(See the editorial commentary by Atmar and Keitel on pages 1211–3 and major article by Omer et al on pages 1216–23.)

Influenza vaccination strategies have targeted elderly individuals because they are at high risk of disease complications and mortality. Statins are a class of drugs used to treat hypercholesterolemia and are frequently used in the elderly population to reduce the risk of cardiovascular disease. However, statins are also known to have immunomodulatory effects that could impact influenza vaccine response. In a post hoc analysis, we performed a cross-sectional observational study nested within a comparative immunogenicity clinical trial of adjuvanted versus unadjuvanted influenza vaccine in elderly persons to evaluate the influence of statin therapy on the immune response to vaccination. Overall, data on >5000 trial participants were available for analysis. Comparison of hemagglutination-inhibiting geometric mean titers to influenza A(H1N1), A(H3N2), and B strains revealed that titers were 38% (95% confidence interval [CI], 27%–50%), 67% (95% CI, 54%–80%), and 38% (95% CI, 28%–29%) lower, respectively, in subjects receiving chronic statin therapy, compared with those not receiving chronic statin therapy. This apparent immunosuppressive effect of statins on the vaccine immune response was most dramatic in individuals receiving synthetic statins. These effects were seen in both the adjuvanted and unadjuvanted vaccine groups in the clinical trial. These results, if confirmed, could have implications both for future clinical trials design, as well as for vaccine use recommendations for elderly individuals.

**Keywords.** statins; influenza vaccine; immunogenicity; elderly.

Statins are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. Because of the association between elevated cholesterol levels and the risk of cardiovascular disease and because of studies showing that statins can lower this risk, statins have been given to large numbers of adults [1]. In fact, it has been estimated that more than one billion people worldwide take statins [2]. Although the primary goal of statin therapy has been to lower cholesterol levels, it has been recognized that this drug class has other effects, including suppression of T-cell activation [3] and immunomodulatory antiinflammatory effects [4]. Since many patients who routinely take statins are elderly and elderly individuals are at higher risk for the complications of influenza [5], we used data from a large comparative immunogenicity study of adjuvanted and unadjuvanted influenza vaccines in elderly individuals in a post hoc analysis to evaluate the influence of statin therapy on the immune response to influenza vaccine.

## METHODS

During the influenza seasons of 2009–2010 and 2010–2011, a randomized, controlled, observer-blind clinical trial was

conducted comparing the safety and immunogenicity of MF-59 adjuvanted trivalent influenza vaccine (aIIV3) and unadjuvanted IIV3 in >14 000 adults aged >65 years of age in Colombia, Panama, the Philippines, and the United States [6]. As part of this evaluation, information on statin use was collected, and this was considered as a potential effect modifier in comparative analyses. Blood samples were obtained on the day of vaccination and 22 days following receipt of seasonally appropriate influenza vaccine. Hemagglutination-inhibiting (HAI) titers were determined using standard methods [7]. For the purposes of our current post hoc cross-sectional observational analysis, patients were classified as receiving statin therapy if they had been taking medication from  $\geq 28$  days before through 22 days after receipt of vaccination. Individuals who had not received statins during this interval were considered to be controls. Patients were further stratified as to whether they were receiving synthetic or natural occurring statins. Geometric mean titers (GMTs) and GMT ratios were then compared between the statin and control groups against the vaccine-homologous influenza virus strains A(H1N1)/California, A(H3N2)/Perth, and influenza B (Brisbane). In adjusted comparisons, an analysis of covariance analysis included the following variables: vaccine group (aIIV3 or IIV3), statin user from  $\geq 28$  days before through 22 days after receipt of vaccination (yes or no), high-risk status (yes or no), sex, log prevaccination titer, and age (both continuous variables). Because an evaluation of the interaction between vaccine type and statins did not reveal an impact of the type of vaccine on the impact of

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statins on the immune response ( $P > .05$ ), ratios of the GMTs in statin recipients and controls were calculated for the unadjuvanted and adjuvanted groups combined. Information on history of receipt of influenza vaccine during prior years was not available. To evaluate the potential influence of this geographic diversity, as well as the impact of prior antigenic exposure by vaccine or wild-type disease on the observed effect of statins, an analysis was conducted in a subset of individuals enrolled in the United States who had prevaccination HAI titers of  $<1:10$ .

## RESULTS

A total of 6961 subjects, 3479 in the MF-59 aIIV3 group and 3482 in the unadjuvanted IIV3 group, had day 22 HAI titers available for analysis. Overall, 2798 and 2786 recipients of aIIV3 and IIV3, respectively, were controls, and 681 and 696, respectively, were determined to satisfy the definition of being statin users. Of the statin users, 76% in the aIIV3 group and 74% in the IIV3 group were taking fermentation-derived statins (pravastatin, simvastatin, lovastatin, and Advicor), and the remainder were taking synthetic statins (fluvastatin, atorvastatin, and rosuvastatin). Overall, 75% of statin users were considered to have a high-risk medical condition. The most common category was underlying neurologic disease, followed by chronic obstructive pulmonary disease (COPD), asthma, congestive heart failure, renal insufficiency, and hepatic disease (Table 1). Overall, 55% of statin users and 68% of controls were male, and 74% of controls and 67% of statin users were between 65–75 years of age, with the remainder being  $>75$  years of age. The results of HAI GMTs against the three influenza vaccine strains are shown in Table 2, with the day 1 ratio adjusted for age, sex, risk group, and vaccine and the day 22 ratio also adjusted for pretiter.

As can be seen in Table 2, individuals receiving statins had higher pretiters against influenza A(H1N1) and influenza B, whereas the reverse was true for influenza A(H3N2). In analyses comparing statin recipients with controls regardless of vaccine type, the GMT ratio was 38% higher in controls for A(H1N1), 67% higher for A(H3N2), and 38% higher for influenza B, indicating a marked apparent reduction in immunogenicity in statin recipients for all 3 antigens despite adjustment for age, high-risk group status, pretiter and type of vaccine received. Similar data were obtained when testing against heterologous strains of influenza B (Malaysia), and influenza A(H3N2) (Brisbane and Wisconsin; data not shown). As expected, post-vaccination day 22 titers were significantly higher in aIIV3 recipients for all 3 antigens [6].

Results stratified by statin type are shown in Table 3.

Patients receiving fermentation-derived statins had higher titers than those receiving synthetic statins, indicating that the latter had a greater apparent immunosuppressive effect on influenza vaccine response. Similar nonstatistically significant trends were also seen in testing against heterologous strains.

**Table 1. Comorbidities in Among Subjects, by Statin (S) and Trivalent Influenza Vaccine (IIV3) Exposure Status**

Comorbidity	S–, Subjects, No. (%)		S+, Subjects, No. (%) <sup>a</sup>	
	aIIV3 (n = 2798)	IIV3 (n = 2786)	aIIV3 (n = 681)	IIV3 (n = 696)
Asthma	120 (4)	112 (4)	42 (6)	43 (6)
CHF	46 (2)	46 (2)	31 (5)	33 (5)
COPD	105 (4)	113 (4)	66 (10)	61 (9)
Hepatic disease	9 (<1)	9 (<1)	4 (<1)	4 (<1)
Neurological disorder	591 (21)	576 (21)	485 (71)	469 (67)
Renal insufficiency	28 (1)	27 (<1)	21 (3)	30 (4)

Abbreviations: aIIV3, adjuvanted IIV3; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; –, nonuse; +, use.

<sup>a</sup> From days –28 to 22.

Since information on prior receipt of influenza vaccine was not available for study participants, to evaluate the potential impact of prior receipt of vaccine on the results, we identified a subset of individuals whose baseline prevaccination HAI titer was  $<1:10$ , assuming that these individuals were less likely to have received vaccine recently. The results for this analysis are shown in Table 4 with a statistically significant reduction being seen in statin recipients for 2 of the 3 antigens.

## DISCUSSION

Within developing countries, life expectancy has been steadily increasing, with an increasing proportion of the populations in developing countries being elderly [8]. Such improvements have been attributed to public health measures, including vaccinations and medications, such as statins [9]. Statins are widely used in adults and elderly individuals for treatment of hypercholesterolemia. We have shown that elderly individuals who receive this class of drugs, especially synthetically derived statins, have apparent lower immune responses to both adjuvanted and unadjuvanted influenza vaccines. Antibody levels achieved with adjuvanted vaccine were higher, so more individuals would reach an arbitrary threshold of protection on statins with aIIV than with IIV. For the influenza A(H3N2) strain tested, while adjuvanted vaccine titers were higher than those for IIV3, titers in statin recipients were lower following aIIV3 receipt than those in controls who received unadjuvanted vaccine.

Given the increasingly complex nature of health interventions in elderly individuals, it will be important to assess potential interactions between such interventions. Although we report on the interaction between statins and influenza vaccination here, other drugs, such as nonsteroidal antiinflammatory drugs, and other vaccines, such as pneumococcal vaccine, commonly used in elderly individuals have the potential for such interactions, as well.

**Table 2. Geometric Mean Titers (GMTs) for Each of 3 Influenza Virus Strains, by Statin (S) and Trivalent Influenza Vaccine (IIV3) Exposure Status**

Strain, Day, GMT	No Statin Use		Statin Use	
	allIIV3	IIV3	allIIV3	IIV3
<b>A(H1N1)/California/09</b>				
	Day 1			
Subjects, no.	2797	2784	681	696
GMT (95% CI)	12 (12–13)	12 (11–12)	22 (19–24)	24 (21–26)
S–/S+ ratio (95% CI)	0.62 (.57–.67)			
	Day 22			
Subjects, no.	2797	2786	681	696
GMT (95% CI)	196 (185–206)	140 (133–148)	170 (155–188)	129 (117–142)
S–/S+ ratio (95% CI)	1.38 (1.27–1.50)			
<b>A(H3N2)/Perth/09</b>				
	Day 1			
Subjects, no.	2797	2784	681	696
GMT (95% CI)	50 (47–53)	49 (46–52)	47 (42–52)	44 (40–49)
S–/S+ ratio (95% CI)	1.13 (1.02–1.25)			
	Day 22			
Subjects, no.	2797	2785	681	696
GMT (95% CI)	669 (638–701)	421 (402–441)	356 (324–392)	209 (190–230)
S–/S+ ratio (95% CI)	1.67 (1.54–1.80)			
<b>B/Brisbane/08</b>				
	Day 1			
Subjects, no.	2798	2786	681	696
GMT (95% CI)	9.6 (9.2–9.9)	9.4 (9.1–9.8)	16 (15–18)	17 (15–18)
S–/S+ ratio (95% CI)	0.68 (.64–.72)			
	Day 22			
Subjects, no.	2798	2786	681	696
GMT (95% CI)	50 (47–52)	43 (41–46)	48 (44–52)	40 (37–44)
S–/S+ ratio (95% CI)	1.38 (1.28–1.49)			

Abbreviations: allIIV3, adjuvanted IIV3; CI, confidence interval; S–, no statin use; S+, statin use.

Our results stand in direct contrast to those of studies of the impact of statins on vaccine immune response to hepatitis A vaccine and tetanus toxoid in young adults. In a study by Seigrist et al, the mean age of subjects was 24 years. In this study, healthy subjects were randomly assigned to receive atorvastatin or placebo. Response to hepatitis A vaccine was assessed 28 days following receipt of vaccine. No difference in the immune response was seen between the 2 groups. It is important to note, however, that in contrast to our study, in which statin recipients were receiving long-term therapy at the time of vaccination, in this hepatitis A study, study participants did not begin statin therapy until the day of vaccination [10]. In another

study, Brantly et al evaluated the response to tetanus toxoid in healthy volunteers. Similar to the hepatitis A study, healthy study participants were randomly assigned to receive atorvastatin or placebo and began treatment on the day of vaccination. Study participants in this study who were assigned to the statin group had 3-fold higher anti-tetanus toxoid immunoglobulin G levels [11]. The 2 clear differences between these studies and the results we report here are the much older age of our study group and the fact that, in the tetanus toxoid and hepatitis A studies, participants had not been chronically exposed to statins at the time of vaccination. It is of course possible that one or both of these factors contributed to the contrasting study results.

**Table 3. Influence of Statin (S) Type on Vaccine Response, as Assessed at Day 22, by Influenza Vaccine Strain**

Homologous Strain	Ratio S–/Ferm S+ (95% CI)	Ratio S–/Syn S+ (95% CI)	Ratio Ferm S+/Syn S+ (95% CI)
B/Brisbane/08	1.32 (1.21–1.43)	1.59 (1.39–1.81)	1.21 (1.05–1.39)
A(H1N1)/California/09	1.31 (1.20–1.44)	1.62 (1.40–1.87)	1.23 (1.05–1.44)
A(H3N2)/Perth/09	1.59 (1.46–1.73)	1.91 (1.68–2.19)	1.20 (1.04–1.39)

Abbreviations: CI, confidence interval; Ferm, fermentation derived; Syn, synthetic; –, nonuse; +, use.

**Table 4. Influence of Statins (S) on the Observed Response to Trivalent Influenza Vaccine (IIV3) in the Subset of Trial Participants in the United States With a Pre vaccination Hemagglutination-Inhibiting Titer of <1:10**

Strain, Day, GMT	No Statin Use		Statin Use	
	allIIV3	IIV3	allIIV3	IIV3
<b>A(H1N1)/California/09</b>				
Day 1				
Subjects, no.	122	128	80	70
GMT	5	5	5	5
Day 22				
GMT (95% CI)	99.6 (77.9–125)	61.3 (47.2–79.5)	82.1 (60.7–111)	46.7 (32.8–66.5)
S–/S+ ratio				
Value (95% CI)	1.19 (.89–1.59)			
P	.240			
<b>A(H3N2)/Perth/09</b>				
Day 1				
Subjects, no.	64	59	43	36
GMT	5	5	5	5
Day 22				
GMT (95% CI)	249 (176–354)	114 (72.1–180)	115 (70.3–189)	69.9 (42.7–114)
S–/S+ ratio				
Value (95% CI)	1.88 (1.18–2.99)			
P	.008			
<b>B/Brisbane/08</b>				
Day 1				
Subjects, no.	124	127	77	67
GMT	5	5	5	5
Day 22				
GMT (95% CI)	22.7 (18.4–28.1)	20.0 (15.8–25.4)	19.4 (15.3–24.7)	14.4 (11.3–18.3)
S–/S+ ratio				
Value (95% CI)	1.28 (1.00–1.65)			
P	.049			

Abbreviations: allIIV3, adjuvanted IIV3; CI, confidence interval; GMT, geometric mean titer; S–, no statin use; S+, statin use.

However, since most statin users take the medication for a long period, the results of these 2 studies have limited use for evaluating the influence of routine statin therapy.

Studies of influenza vaccine effectiveness in elderly individuals have revealed suboptimal levels of effectiveness. In a study by Monto et al in elderly nursing home patients, vaccine effectiveness was 33% against influenza-like illness and 43% against pneumonia [12]. In an earlier meta-analysis of data from 20 observational studies that were largely conducted during the 1970s and 1980s, Gross et al found higher pooled estimates of vaccine efficacy of 56% (95% confidence interval [CI], 39%–68%) for prevention of respiratory illness, 53% (95% CI, 35%–66%) for prevention of pneumonia, 50% (95% CI, 28%–65%) for prevention of hospitalization, and 68% (95% CI, 56%–76%) for prevention of death [13]. Of interest is that estimates of efficacy against respiratory illness and pneumonia in the earlier years, when statin use was less common, are higher than those in the more recent study. It is also possible that these differences are due to different influenza virus strains and other population factors.

This study was a post hoc analysis, and as such the study has potential limitations. Since the receipt of statins was not randomly assigned, it is possible that the observed effect could be due to other factors. However, as noted above, studies that have attempted to randomly assign statin therapy have been limited for logistical reasons to short-term statin therapy and hence have limited generalizability because most individuals receiving statins take them for the long term. It is possible that individuals receiving statins are more likely to have received IIV3 in the years before this study. Receipt of influenza vaccine in the previous season has been associated with a decreased immune response in the subsequent season. Since we did not have information available on prior influenza vaccination history from this trial, we analyzed the subset of patients with prevaccination HAI titers of <1:10, reasoning that these individuals were less likely to have either experienced influenza virus infection or received an influenza vaccine with that antigen recently. Although power was limited in this analysis, we saw the same effect of statins on vaccine response in this subset, with results being statistically significant for 2 of the 3 antigens. In addition,

since individuals with chronic conditions are more likely to seek medical care more often, we adjusted for the presence of chronic conditions in study participants in the main analysis. However, any future prospective studies of vaccine-induced immune response should consider obtaining prior vaccination history and taking this into account in the analysis. Many of the patients enrolled in the trial were from outside the United States. However, even though power was limited, we observed substantially the same impact of statins on the immune response to vaccination when the analyses were limited to subjects only in the United States (data not shown). Data for US subjects with HAI pretiters of <1:10 are shown in Table 4.

Statins have been considered as adjunct agents in the prevention of pneumonia because their immunosuppressive effect might lower baseline inflammatory status and, thus, the severity of pneumonia. Observational studies of statin use in COPD have reported reductions in mortality of 30%–50% following pneumonia or infective exacerbations in statin users [14]. Other studies have not found an impact of statins on pneumonia and sepsis risk [15]. Fedson has recommended consideration of statins as therapeutic agents in the treatment of pneumonia in elderly individuals [16]. In a commentary, he states that, while system biologists have suggested the use of immunomodulatory agents such as statins in the treatment of influenza, randomized clinical trials of this approach should precede their routine use of this. Fedson similarly points out that, especially in pandemics, where severe disease may precede vaccine availability by many months, consideration should be given to evaluating statins as potential agents to reduce inflammation and hence severity of disease [17].

Clearly, the impact of statins on the immune system and consequent vaccine response, as well as disease risk, are complex. While the immunosuppressive effects of statins may be desirable in the acute disease state, the same effect could be deleterious if it impacts vaccine response. We have shown that long-term statin therapy is associated with an apparent reduced response to influenza vaccine in elderly individuals. This observed negative effect should be taken into account when evaluating the immunogenicity of influenza vaccines in elderly individuals in the future. If these results are confirmed by other studies, these results could support preferential use of

adjuvanted vaccines or high-dose influenza vaccines in elderly individuals to counteract statin-induced immunosuppression.

## Notes

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