Pandemic Influenza: A Potential Role for Statins in Treatment and Prophylaxis

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The next influenza pandemic may be imminent. Because antiviral agents and vaccines will be unavailable to people in most countries, we need to determine whether other agents could offer clinical benefits. Influenza is associated with an increase in acute cardiovascular diseases, and influenza viruses induce proinflammatory cytokines. Statins are cardioprotective and have anti-inflammatory and immunomodulatory effects, and they thus might benefit patients with influenza. This hypothesis should be evaluated by using administrative databases to search for reduced rates of hospitalization and death due to influenza-related conditions among people taking statins. These studies should be followed by laboratory studies of statins in animal and cell-based models of influenza virus infection and, later, by clinical trials. Positive results from such studies would provide physicians in all countries with something to offer patients for treatment and prophylaxis of pandemic influenza. Generic statins will be widely distributed and inexpensive. They might be the only agents that could alter the course of a global pandemic.

Influenza experts and health officials throughout the world are extremely concerned about global spread of avian H5N1 influenza and the possibility that it could lead to the next pandemic [1, 2]. If a pandemic like the 1918 pandemic were to occur today, it would kill 175–350 million people worldwide [3]. If the case-fatality rate associated with the next pandemic is like that associated with the human cases of H5N1 influenza recently seen in Southeast Asia, it would kill even more people [4]. Speculation like this may seem farfetched, but avian influenza viruses have caused devastating outbreaks of disease in mammalian species other than man. In the early 1980s, for example, an avian H7N7 influenza epidemic killed ~20% of the harbor seals living along the North Atlantic coast [5].

We cannot predict whether the next influenza pandemic will be mild, like the 1968 pandemic; moderate, like the 1957 pandemic; severe, like the 1918 pandemic; or overwhelmingly catastrophic [6]. We can be certain, however, that it will occur sooner or later. When this happens, we will have very limited supplies of antiviral agents [4], and antiviral resistance might compromise their usefulness against H5N1 influenza viruses [7]. Moreover, we will have to wait many months before limited supplies of vaccines become available [8]. If an H5N1 influenza pandemic is imminent, prospects for obtaining adequate supplies of antigen-sparing pandemic vaccines are becoming increasingly remote [9]. Practically speaking, most people in the world will have little or no access to antiviral agents or vaccines. For this reason, we need to determine whether currently available agents could be used for treatment and prophylaxis of pandemic influenza.

INFLUENZA, CARDIOVASCULAR DISEASES, AND CYTOKINES

Influenza virus infections are associated with an increase in acute cardiovascular and cerebrovascular (hereafter called "cardiovascular") diseases, and the winter-season mortality associated with these events is greater than that ascribed to influenza-related pneumonia and other respiratory conditions [10, 11]. When influenza is prevented by vaccination, hospitalizations and deaths due to influenza-related cardiovascular diseases are reduced [10, 12].

Influenza viruses are potent inducers of many biological response mediators that make up the innate immune system [13]. In both experimental [14, 15] and naturally occurring [16] human influenza virus infections, increased serum levels of several proinflammatory cytokines (e.g., TNF-α and IL-6) have been positively correlated with the symptoms of clinical illness. In an experimental model of human influenza A virus infection, H3N2 viruses were shown to be more potent inducers

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of TNF-α and IL-6 than were H1N1 viruses [17]. The avian H5N1 influenza viruses that have caused fatal disease in humans are exceptionally potent inducers of proinflammatory cytokines [18–21]. Cytokine dysregulation is now regarded as a major contributor to the severe pathophysiological changes seen in human disease caused by the avian H5N1 [2, 18–21] and 1918 pandemic influenza viruses [22, 23].

ANTI-INFLAMMATORY AND IMMUNOMODULATORY EFFECTS OF STATINS

Inflammation plays an important role in the pathogenesis of all stages of cardiovascular diseases [24, 25]. Proinflammatory cytokines reduce the beneficial effects of endothelial nitric oxide synthase and thrombomodulin that help maintain normal blood flow [25]. They also increase expression of surface adhesion molecules (e.g., vascular cell adhesion molecule–1) that recruit leukocytes to vessel walls. Leukocytes, in turn, elaborate proinflammatory factors (e.g., C-reactive protein, IL-6, and soluble CD40 ligand) that set the stage for acute intravascular thrombosis. During these events, increased levels of several cytokines can be demonstrated in patient serum samples.

The clinical benefits of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) for patients with cardiovascular diseases are firmly established. A recent meta-analysis of 90,056 individuals enrolled in 14 randomized controlled trials showed that, over a 5-year period, statins were associated with a 21% reduction in major cardiovascular events, including a 19% reduction in mortality associated with coronary events and a 17% reduction in fatal or nonfatal stroke [26]. This level of protection was observed not only because statins reduce levels of low-density lipoprotein cholesterol but also because they have a wide variety of anti-inflammatory and immunomodulatory effects [25].

Statins improve endothelial cell function by decreasing cellular adhesion (decreased vascular cell adhesion molecule–1) and thrombosis (decreased tissue factor) and increasing vasoreactivity (increased endothelial nitric oxide synthase). They affect immune and inflammatory cells by reducing monocyte and macrophage recruitment and the expression of numerous cytokines and chemokines (e.g., IL-1, IL-6, TNF-α, IFN-γ, RANTES [regulated on activation, normally T cell expressed and secreted], and soluble CD40 ligand). They also inhibit smooth muscle cell proliferation and platelet hyperreactivity.

At the molecular level, statins interact with the synthesis of isoprenylated proteins that serve as lipid attachments for small guanosine triphosphate–binding Ras and Ras-like (e.g., Rho and Rac) proteins. Through their actions, they improve vascular function (increased endothelial nitric oxide synthase) and decrease leukocyte adhesion and fibrinolytic activity. In addition, they affect nuclear events that regulate gene expression and cell function. Proinflammatory stimuli cause Rho and Rho-like proteins to induce nuclear factor–κB (NF-κB), which then translocates to the cell nucleus and induces the expression of target genes, including those for several cytokines. Statins limit these activities.

Statins also reduce the expression of regulatory proteins that compose the activator protein 1 complex and induce the expression of other nuclear factors (e.g., Kruppel-like factor–2) that exert broad effects on endothelial cell function (increased endothelial nitric oxide synthase and decreased vascular cell adhesion molecule–1). These activities counterbalance those of NF-κB. Statin-mediated induction of endothelial nitric oxide synthase and thrombomodulin depends on Kruppel-like factor–2 [25].

A large body of evidence now suggests that the long-term cardiovascular benefits of statins are associated with their anti-inflammatory and immunomodulatory effects [24, 25]. However, statins can also induce remarkable short-term improvements in cardiovascular function. For example, the use of short-term, low-dose simvastatin treatment for patients with nonischemic dilated cardiomyopathy resulted in clinical improvement that was associated with substantial reductions in serum levels of several inflammatory mediators, including TNF-α and IL-6 [27]. The anti-inflammatory effects of pravastatin on coronary endothelial dysfunction [28] and of simvastatin on C-reactive protein levels [29] have been demonstrated in patients even after administration of a single dose. Moreover, an epidemiological study of >300,000 patients with acute myocardial infarction has shown that those who continued receiving or were newly receiving statins within 24 h of hospitalization had a >3-fold reduction in mortality, compared with patients who were not treated [30]. These short-term effects of statins might have important implications for the management of other acute life-threatening events associated with inflammation.

STATINS, ACUTE LIFE-THREATENING INFECTIONS, AND BACTERIAL SEPSIS

In addition to their effects on cardiovascular diseases, there is growing evidence that statins could be beneficial in the treatment of patients with life-threatening infections, some of which are associated with cytokine dysregulation. For example, in infants with bacterial sepsis, serum levels of several proinflammatory cytokines were higher than they were in infants with culture-negative sepsis syndrome, and levels were highest in those infants who died [31]. In adults with sepsis, depressed myocardial contractility was associated with increased levels of several proinflammatory cytokines, and serum samples obtained from these patients activated transcription factors and induced human fetal cardiac myocyte apoptosis [32].

Experimental studies suggest that statins favorably alter the course of bacterial sepsis. In a murine model of acute bacterial sepsis (cecal ligation and puncture without subsequent administration of an-

tibiotics), prophylaxis [33] and treatment [34] with simvastatin dramatically preserved cardiac and hemodynamic function and significantly prolonged survival. In addition, 3 clinical reports have suggested that statins were of benefit in patients with acute bacterial sepsis (table 1) [35–37]. The first study included 388 patients who were hospitalized with gram-negative or *Staphylococcus aureus* bacteremia [35]. The second study included 361 patients who were hospitalized with presumed or documented acute bacterial infections [36]. The third study included 438 patients who were hospitalized with bacterial sepsis [37]. Remarkably, if statin treatment was continued in the hospital, the rate of death attributable to bacteremia was reduced by 87% in the first study [35] and 92% in the third study [37]. In addition, a population-based, nested, case-control study of 69,168 elderly patients discharged after hospitalization for acute cardiovascular events showed that the risks of subsequent hospitalization for sepsis and for fatal sepsis were lower for statin-treated patients than they were for untreated control patients (table 1) [38]. Another population-based study did not find a beneficial effect of statins on 30-day sepsis-associated mortality, but the number of statin-treated patients was small and the 95% CIs around the point estimates were very broad (table 1) [39]. Many physicians have begun to ask whether treatment of sepsis should include statins [41].

The mechanism(s) by which statins exert beneficial effects in patients with bacteremia and sepsis are not well understood. Animal models of acute lipopolysaccharide-induced sepsis (similar to endotoxemia) and bacterial sepsis have shown that a variety of inflammatory mediators are implicated in fatal disease [42]. Nonetheless, many treatment interventions targeting specific abnormalities suggested by animal studies (e.g., TNF-α) have not been efficacious when tested in clinical trials in humans. To date, only low-dose corticosteroids and activated protein C have been shown to benefit patients with severe sepsis [42]. However, several newer therapeutic targets are now being considered, including Toll-like receptors, high-mobility group box 1 protein, macrophage migration inhibitory factor, complement C5a and C5a receptors, and inhibitors of apoptosis [43, 44]. Statins have effects on several of these targets.

STATINS, ACUTE LUNG INJURY, AND INFLUENZA

Cytokines also act as inflammatory mediators in acute lung injury, as shown in both experimental and clinical studies [45–49]. In a recent report, simvastatin dramatically reduced the response of human pulmonary artery endothelial cells to thrombin-induced endothelial barrier and cytoskeletal dysfunction, an effect that required gene expression and protein synthesis [50]. Simvastatin also induced pronounced endothelial barrier protection in a murine model of acute lung injury caused by intratracheal administration of lipopolysaccharide [51]. In this model, simvastatin significantly altered lipopolysaccharide-mediated expression of several genes associated with inflammatory change (e.g., IL-6 and Toll-like receptor 4). In another model of acute lung injury in rats after intestinal ischemia and reperfusion, pretreatment with simvastatin was associated with reduced leukocyte infiltration into lung tissue, decreased pro-

Table 1. Observational studies showing the protective effects of statins in patients with bacteremia, sepsis, or pneumonia.

Principal investigator [reference]	No. of statin users[a]/ no. of nonusers	Outcome	Adjusted OR/HR[b] (95% CI)
Liappis[c] [35]	35[d]/353	Bacteremia-associated in-hospital mortality	0.13[e] (0.02–0.99)
Almog[f] [36]	82[g]/279	Development of severe sepsis	0.13 (0.03–0.52)
	37[g]/324	ICU admission	0.30 (0.10–0.95)
Kruger[c] [37]	66[d,g]/372	28-day bacteremia-associated mortality	0.29 (0.10–0.82)
	56[d]/372	28-day bacteremia-associated mortality	0.08 (0.01–0.60)
Hackam[h] [38]	34,584[g]/34,584	Development of sepsis	0.81 (0.72–0.90)
		Fatal sepsis	0.75 (0.61–0.93)
Thomsen[i] [39]	176[g]/5177	30-day bacteremia-associated mortality	0.93 (0.66–1.30)
Mortensen[c] [40]	110[g]/677	30-day pneumonia-associated mortality	0.36 (0.14–0.92)

NOTE. HR, hazard ratio; ICU, intensive care unit.

[a] Use of any statin.

[b] Risk adjustment strategies varied and included demographic factors, comorbid conditions, clinical and laboratory findings, and concurrent medications. See original references for details.

[c] Retrospective cohort study of hospitalized patients.

[d] Continued use in hospital.

[e] The OR for this study [35] was calculated as the reciprocal of the OR reported in the original publication.

[f] Prospective cohort study of hospitalized patients.

[g] Prior use.

[h] Population-based nested case-control study using administrative data.

[i] Population-based cohort study using administrative data.

duction of free oxygen radicals, and reduced severity of acute lung injury [52].

Clinical studies of healthy elderly people have shown that those with elevated levels of proinflammatory cytokines (TNF-α and IL-6) have an increased risk of being admitted to the hospital later for community-acquired pneumonia [53]. Moreover, among hospitalized patients with pneumonia, those with elevated proinflammatory cytokines have an increased risk of developing septic shock [54]. A recent retrospective study of 787 patients with community-acquired pneumonia showed that 30-day mortality was reduced by 64% among those who were previously taking statins (table 1) [40]. The anti-inflammatory and immunomodulatory effects of statins on the host response to acute lung injury are becoming increasingly evident.

Given the clinical associations between influenza and cardiovascular diseases and the cytokine-mediated inflammatory changes associated with both, is it possible that the benefits of statins, so evident for cardiovascular diseases, bacteremia, sepsis, and pneumonia, might also extend to patients with influenza? To date, no reports have been published describing the direct effects of statins on the molecular and clinical pathophysiological profiles of experimental or clinical influenza virus infections. Nonetheless, the findings outlined above suggest the possibility that treatment and prophylaxis with statins might alter the clinical course and outcome of interpandemic and pandemic influenza [55].

EPIDEMIOLOGICAL EVALUATION OF THE STATINS/INFLUENZA HYPOTHESIS

This hypothesis could be evaluated in several ways. Initially, the most direct and, probably, most efficient approach would be to look for epidemiological signals of the protection provided by statins against influenza-related events in populations during interpandemic years. For example, cardiologists could evaluate the occurrence of these events in treated and control subjects who have participated in large, prospective, randomized controlled trials of statins. Unfortunately, these studies might not be conclusive, because patients enrolled in the trials have been younger, rather than older, adults and have experienced relatively few hospitalizations or deaths due to respiratory conditions [26].

As an alternative, investigators could follow the epidemiological model of the statins/sepsis study mentioned above [38] and undertake retrospective cohort and case-control studies of the effects of statins in people whose health care and medical treatments have been documented in large administrative databases. The primary goal of these studies would be to see whether there were differences between untreated and statin-treated subjects, with regard to rates of influenza-related hospitalization and death, especially those due to pneumonia and influenza and other respiratory conditions. The outcomes would need to be evaluated during and outside of influenza seasons, and careful adjustment for confounding variables, including influenza vaccination, would be essential.

It is hoped that the epidemiological studies would show a benefit of statins on influenza-related outcomes. However, they might show that statin treatment could be harmful. For example, statins could impair host defenses and lead to an increase in secondary bacterial pneumonias [56], or they could down-regulate cytokines and lead to uncontrolled virus replication and increased mortality [23]. Alternatively, discontinuation of statin treatment could be quickly followed by clinical deterioration [37], as has been shown by the rapid loss of statin-induced anti-inflammatory and immunomodulatory effects in experimental models of endothelial dysfunction [57] and stroke [58]. Whatever the epidemiological findings, they could be used to generate hypotheses for a wide range of laboratory and clinical studies.

Two epidemiological studies have been undertaken to test the statin/influenza hypothesis. One study has been conducted by investigators in The Netherlands, who have used a large general practice administrative database. The other has been conducted by Swiss investigators, who have used the United Kingdom's General Practice Research Database. The Swiss investigators recently completed a population-based, nested, case-control study of pneumonia (R. G. Schlienger and C. M. Meier, personal communication). They studied cases that occurred throughout the year, not just those that occurred during influenza seasons. They found that people who were currently taking statins (defined as statins having been prescribed within 30 days of the date of onset of pneumonia) had a statistically significant reduced risk of 30-day pneumonia-associated mortality and a lower but not quite statistically significant risk of being hospitalized with pneumonia and surviving. Protection was not shown for those who had taken statins in the past (defined as statins having been prescribed $\geqslant$30 days before the date of onset of pneumonia) but were currently not taking them, nor was it shown for those who had taken a control medication at any time. Preliminary findings from the Dutch epidemiological study have also suggested that statin treatment was associated with reductions in influenza-related pneumonia, acute myocardial infarction, and stroke [59].

LABORATORY AND CLINICAL EVALUATION OF THE STATINS/INFLUENZA HYPOTHESIS

The results obtained from the 2 epidemiological studies mentioned above can only suggest that patients who are treated with statins for the prevention of cardiovascular diseases are also protected against respiratory diseases often associated with influenza. Given the limitations of the data available to investigators, the studies could not determine whether statin treatment was continued after hospital admission, although, in many instances, it probably was [37].

The "epidemiological signals of protec-

tion" obtained in the Swiss and Dutch studies need to be confirmed in other population-based studies. Nonetheless, together with the clinical studies summarized in table 1, they provide enough evidence to justify undertaking laboratory studies of statin treatment and prophylaxis in animal models of influenza caused by interpandemic (H3N2) [60], avian H5N1 [61], and 1918 pandemic–like [23, 62] viruses. The challenge viruses should include related reassortants with different degrees of virulence. Wherever possible, the studies should evaluate the effects of statins on the cellular and molecular manifestations of disease and should compare the results with their corresponding gene expression profiles [63, 64]. Special attention should be given to the effect of statins on secondary bacterial pneumonia [65]. The results of these studies will need to be cautiously interpreted, as is indicated by experience gained in interpreting the conflicting results of animal model and human studies of therapeutic interventions for sepsis [42].

If animal studies of influenza indicate that statins are protective, investigators should explore the molecular effects of statins in influenza virus–infected cells. Cholesterol synthesis is essential for the normal functioning of cell membranes, especially lipid rafts [66]. Cholesterol is also essential for influenza virus assembly, budding from raft-derived microdomains, and virus infectivity for other cells [67–69]. Experimental studies in mice have shown that Toll-like receptor 7, which is located in the endosomal compartment of the cell, recognizes single-stranded influenza virus RNA [70]. Once recognized, Toll-like receptor 7 recruits several adaptor molecules (e.g., myeloid differentiation protein 88 [MyD88]) that, through a series of signalling steps, lead to the translocation of NF-κB to the nucleus, an essential event in establishing influenza virus infection [71]. The "MyD88-dependent pathway" controls gene expression for several proinflammatory cytokines and chemokines (e.g., TNF-α, IL-6, and IL-1β), type 1 interferons, plasmacytoid dendritic cell maturation, and antiviral immunity [70]. These and many other intracellular signalling cascades have been identified in cells infected with influenza virus [72].

One of the most important intracellular signalling pathways involves influenza virus–induced caspase activation and subsequent apoptosis. Caspase 3 activation is essential for influenza virus replication. Apoptosis is thought to be responsible for the induction of lymphocyte depletion (prominent in human H5N1 influenza virus infection [4]) and the down-regulation of proinflammatory cytokines. The overall host benefits of apoptosis, however, are still uncertain [72]. From what is already known, statins have the potential to affect many of these and other molecular pathways in influenza virus–infected cells [25].

Clinical investigators also should begin to gather information on cytokine profiles and levels of other potential immunomodulatory molecules (e.g., high-mobility group box 1 protein [73], hyaluron degradation products [74], and angiopoeitin-2 [75]) in patients with seasonal and avian H5N1 influenza, giving attention to establishing correlates with disease severity and prognosis. Eventually, they might begin planning clinical trials of statin treatment and prophylaxis. Studies of statin safety, as well as statin efficacy, in children would be especially important. Physicians caring for patients with life-threatening avian H5N1 infections could even consider treating such patients with statins on a compassionate basis.

Statins might not be the only medication useful in the treatment and prophylaxis of pandemic influenza. Epidemiologists, laboratory investigators, and clinicians should look for evidence that other existing agents, such as angiotensin-converting enzyme inhibitors [76], angiotensin II receptor blockers [77], aldosterone antagonists [78], or phosphodiesterase inhibitors [79], might be beneficial, either alone or in combination. Ideally, these agents should be generically produced, widely available in developing countries, and inexpensive. Research on statins and other agents might also have relevance for other serious virus diseases, such as severe acute respiratory syndrome [80–82] and HIV/AIDS [83].

THE COMPELLING PUBLIC HEALTH RATIONALE FOR CONSIDERING STATINS FOR PANDEMIC INFLUENZA

When the next pandemic arrives, physicians who live in countries without antiviral stockpiles or vaccine companies will have little or nothing to offer their patients. If epidemiological, laboratory, and clinical studies confirm the benefits of statins for the treatment of influenza, physicians everywhere will have something to offer their patients for the pandemic. Statins are already widely distributed throughout the world and are used to treat millions of people on a year-round basis. Moreover, the patents for several statins will expire in a year or two, and several are already being produced as generics in some developing countries. The cost advantage of statins, compared with existing antiviral agents, will be remarkable. Currently, in the United States, a 5-day course of the antiviral agent oseltamivir costs ~$60–$90, whereas a 5-day course of generic simvastatin will cost as little as $1.75 [84]. In developing countries, the cost advantage of generic statins will be even greater.

The scientific rationale for considering statins for treatment and prophylaxis of pandemic influenza is persuasive, but the public health rationale is overwhelmingly compelling. Given their low cost, safety, and worldwide availability, generic statins could become crucially important for confronting the next pandemic. They could greatly reduce the disparity that will otherwise separate developed and developing countries. They could become the only currently available agents to alter the course of what otherwise might become an unprecedented global health crisis. For public health reasons alone, the research agenda outlined in the present report is one that we cannot afford *not* to under-

take, and we must do so with a great sense of urgency.

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