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The Use of Statins and Risk of Community-Acquired Pneumonia

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Abstract
Purpose of the Review Community-acquired pneumonia (CAP) is still associated with a large burden and causes significant morbidity and mortality. Besides universal vaccination and antibiotic treatment, statins as adjunctive therapy may also have a beneficial role in the prevention and treatment of CAP. Our goal from this review is to discuss the epidemiology of CAP, and role of statins as adjunctive therapy in the development of CAP.
Recent Findings Statins are lipid-lowering medications characterized by their ability to control hypercholesterolemia in addition to other pleiotropic effects that could explain their role in the pathogenesis of CAP. While most observational studies have shown that statins reduce risk of pneumonia in the general population, patients with diabetes, and recently in patients with myocardial infarction, no randomized controlled trial (RCT) to date has been conducted to assess the efficacy of statins to prevent development of CAP.
Summary Given the paucity of robust randomized evidence to assess statin use and the development of CAP, and considering conflicting results of the observational studies, we are not in favor of initiation of statins for either the prevention or treatment of CAP.

Keywords Community-acquired pneumonia (CAP) · Adjunctive therapy · Statins

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Introduction

Despite advances in medical management, availability of potent antimicrobial therapies, and the establishment of intensive care unit facilities [1, 2], community-acquired pneumonia (CAP) is still associated with significant morbidity and mortality, and substantial healthcare costs secondary to hospitalization and management [3]. Besides universal vaccination and antibiotic treatment, various adjunctive therapies have been investigated with agents that target different or specific components of disease pathogenesis, which represents a potential strategy to reduce CAP-related mortality and improve poor outcomes [1, 2, 4]. The four major adjunctive therapies are macrolide agents, corticosteroids, antiplatelet therapies, and statins [3]. Statins are lipid-lowering drugs used in the prevention of cardiovascular diseases. However, they may also have a beneficial role in the prevention and treatment of CAP [5], in addition to their cardiovascular effects [6, 7]. This review discusses briefly the epidemiology of CAP and expands the role of statins as an adjunctive therapy in the development of CAP.

Epidemiology of Community-Acquired Pneumonia

Globally, CAP remains a leading cause of hospitalization and mortality. Global burden of disease study 2013 estimated that lower respiratory tract infection (LRTI)

was the second cause of mortality, and life lost in 2013 [8]. Incidence and mortality from CAP vary widely by age, geographic region, and population at risk among other factors. In the USA for example, the annual incidence of adults hospitalized for CAP in Chicago and Nashville is estimated to be 24.8 cases per 10,000 adults, with higher incidence rates reported in elderly populations [9]. McLaughlin et al. have found that the annual mortality rate reaches 36% in high-risk patients at least 65 years of age with immunocompromising conditions when analyzing data from the US Veterans Health Administration [10]. Additionally, the annual CAP expenditure was estimated as $750 million [10].

In the Netherlands, the incidence rates of CAP were estimated to be 295 per 100,000 individuals per year according to a four-year retrospective study [11]. Around two-thirds of the cases were hospitalized, and 5.9% were admitted to the intensive care unit for at least one night. The total cost for these CAP cases was estimated to be 711 million euros [11]. Likewise, in the UK, the incidence of CAP increased significantly from 4.2% per year between 1998 and 2008 to 8.8% per year between 2009 and 2014 [12•].

In Asia, a study from Japan estimated the incidence of CAP to be 16.9 per 1000 patient-years in patients at least 15 years older. The rate of hospitalization was 5.3 per 1000 patient-years, and the in-hospital mortality was 0.7 per 1000 patient-years [13].

The incidence rates were much higher among the elderly, with 10-fold higher incidence rates among those at least 85 years of age and older [13].

Pathophysiological Mechanisms of Statins and Development of CAP

Statins are lipid-lowering medications that inhibit cholesterol biosynthesis in the liver by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMB-CoA) reductase. Statins are mainly used for the prevention and treatment of atherosclerotic cardiovascular disease. They are characterized by their ability to control hypercholesterolemia in addition to other pleiotropic effects, such as improving vascular endothelial function and immunomodulatory, antiinflammatory, and antiplatelet actions. These effects could explain the role of statins in the pathogenesis of CAP [14].

CAP can cause severe respiratory and systemic inflammation [15]. High inflammatory mediator levels are an important cause of treatment failure and mortality. Inhibiting the activity of HMB-CoA enzyme by statins leads to a reduction in the synthesis of cholesterol and isoprenoids [16]. In the case of isoprenoids, isoprenylation defects affect the signaling pathways involving G-protein-coupled receptors (GPCRs) on immune/inflammatory cells and platelets, thus reducing the pro-inflammatory activities of these cells. In the case of cholesterol, reducing the cholesterol on the plasma membranes of inflammatory and immune cells counteracts the cytotoxic and pro-inflammatory activities of the cholesterol-binding pore-forming toxin [17]. Statins can also reduce both the pulmonary production of chemokines as well as the systematic levels of tissue necrosis factor (TNF-α), Interleukin(IL)-6, or C-reactive protein (CRP). This suggests additional antiinflammatory benefits of statins in CAP patients [18, 19].

Statins have also been reported to suppress platelet activity [20]. The intracellular signaling by other types of GPCR [20] and the lectin-like oxidized low-density lipoprotein-1 receptor (LOX-1) depends on intact lipid rafts (i.e., subdomains of the plasma membrane that contain high concentrations of cholesterol and glycosphingolipids), which might be disrupted via the cholesterol-lowering activity of statins [21]. Decreasing the scavenger receptors (LOX-1) expressed on platelets is one of the mechanisms of the antiplatelet activities of statins [22]. Other mechanisms that suppress antiplatelet activities independently of cholesterol-lowering activity might include increased production of the enzyme endothelial nitric oxide synthase (eNOS) by platelets, inhibition activity of phospholipase A2, and decreased expression of pro-adhesive CD40L [23].

Several experimental studies assessed other alternative mechanisms of statins, which reported different immunomodulatory effects of statin use on cytokine expression and secretion, neutrophil function, and pulmonary integrity [24]. These immunomodulatory effects might be beneficial in the treatment of CAP, but not all mechanisms are fully explained. However, there were contradicting results between experimental and clinical studies on the immunomodulatory effects of statins, the host, and the various causative pathogens. In animal models, statins were protected against disruption of vascular integrity after *Streptococcus pneumoniae* [24], while they caused a significant increase in pulmonary inflammatory cell infiltration after *Chlamydia pneumoniae* [25]. However, in clinical observations, *S. pneumoniae* generally produces a more severe inflammatory response than C. *pneumoniae* [24].

It still remains unclear whether types of statins can be correlated with different antiinflammatory effects. A previous study showed that simvastatin, fluvastatin, and atorvastatin had similar effects on reducing the risk of incident pneumonia in myocardial infraction (MI) patients [26••]. Likewise, in the general population, simvastatin and atorvastatin were found to have similar associations with the risk of pneumonia [27]. Furthermore, statins have dose-dependent antiinflammatory effects [28, 29]. Thus, the optimal intensity of statins regarding their antiinflammatory and pleiotropic effects is still unknown.

Role of Statins in the Development of Community-Acquired Pneumonia

Several observational studies have tried to assess the association between statin use and the development of CAP. Studies have reported outcomes associated with statin use in patients with bacteremia, sepsis, or even CAP. However, Van de Garde et al. [30] was the first study to investigate the use of statin and the risk of the development of CAP in a large retrospective case-control study. They found that the use of a statin conferred a protective effect for the development of CAP [30]. Another study reported from the same general practice database reported a reduced risk for fatal pneumonia but there was no effect on uncomplicated CAP [31]. A different study interrogated another general practice database in England and a beneficial role of statins to prevent the development of CAP [32]. Kwong et al. [33] looked at a large population-based cohort over a period of 10 influenza seasons. They found that statin use was associated with a protective effect for influenza morbidity which was manifested as reduced hospitalization due to CAP and its associated mortality [33]. In a large population-based nested case-control study, exposure to statins was found to have a protective effect for the development of CAP [34]. Smeeth et al. also have reported a beneficial effect of statins in the development of pneumonia from a population-based cohort study [35].

Nielsen et al. [36] also conducted the largest combined population-based case-controlled study thus far to assess statin use and the risk of pneumonia in Denmark. They found that statin use was associated with a reduced risk of hospitalization for CAP. Almost all the studies were retrospective in nature and affected by various confounders. Also, a study found that most of the variability encountered in these studies was because of the selection of cases and controls and the ascertainment of exposure to statins. Dublin et al. [37] attempted to address these confounders in a population-based case-control study. Not only did their findings not conform to the results of the other studies, but also found an increased risk of CAP with the use of statins. However, when adjusting for the potential confounders included in Dublin et al. study, Nielsen et al. found that statin use changed from a harm to a benefit [36]. This inconsistency may be due to differences in the available information on potential confounders, or they may indicate that the possible healthy-user effect associated with statin use is weaker in the study by Nielsen et al. [36].

While previous studies have shown a reduced risk of pneumonia in the general population and in patients with diabetes, Lin et al. [26••] assessed whether statin use is associated with a reduced risk of incident pneumonia in MI patients. In this retrospective study, statin users had a 15% reduced risk of pneumonia requiring hospitalization among MI patients [26••]. The benefits of statins were also particularly marked within 3 months. However, this favorable effect was not significant when the analysis was limited to MI patients with a higher $CHADS_2$ (i.e., congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and prior stroke (double weight)) score ≥ 2. Moreover, the data were obtained from prescription claims in a health database that lacked information on tobacco use and ambulatory status, which could both contribute to the risk of pneumonia. In a report from the large JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), treatment with rosuvastatin was associated with a reduced risk of incident pneumonia in comparison to subjects that received a placebo [38]. However, interpretation of the results should be performed with caution since the treatment did not appear to reduce the risk of severe infections, all infections, or sepsis. This could indicate that the apparent benefits in pneumonia may have been due to chance. Furthermore, these outcomes are secondary endpoints, and the trial was not primarily designed to investigate the outcome of interest. Table 1 summarizes the studies investigating the roles of statins in the development of CAP.

To date, no randomized controlled trial (RCT) has been conducted to assess the efficacy of statins to prevent the development of CAP. However, a few observational studies and RCTs have assessed the therapeutic efficacy of statins in patients diagnosed with pneumonia. Hospital length of stay (LOS) can be used as an indicator for time to clinical stability, and shorter LOS positively impacts the cost and risk of adverse nosocomial events [39]. In a large prospective study, Havers et al. [40•] found no evidence to suggest that statin use prior to and during hospitalization improved hospital LOS or in-hospital mortality among CAP patients. Viasus et al. [41••] investigated the time to clinical stability and level of inflammatory markers in patients with CAP who received simvastatin versus placebo; they found no difference in either end-point between statin users and non-users. However, the study was inconclusive as it was stopped prematurely and did not reach an adequate sample size. In another trial, simvastatin was not found to decrease mortality in patients with suspected ventilator-associated pneumonia. Additionally, other RCTs have tested the pleiotropic effect of statins on a panoply of infections and sepsis. These RCTs also fail to delineate clearly the role of statins and have been limited by conflicting results, which range from a decrease in levels of inflammatory markers to no difference, and from presumed clinical efficacy to no clinical benefit.

As mentioned, numerous studies have been reported which have addressed the association of the use of statins and the subsequent development of CAP and its related outcomes. However, these studies have been limited by the difference in populations studied in terms of age and associated co-morbidities. There was a lack of a standardized definition of pneumonia, and the definition relied on the diagnosis by a general physician, which may or may not have been supplemented by

Table 1 Characteristics of the studies which investigated statin use and the development of community-acquired pneumonia (reproduced with permission from Khan, A.R., et al., *The role of statins in prevention and treatment of community acquired pneumonia: a systematic review and meta-analysis.* PloS one, 2013. **8**(1): p. e52929)

Study; study period	Study design	Setting	Ascertainment of statin use	Cases/controls, n; confounders adjusted	Adjusted effect estimate
Van De Garde et al.; 1987–2001	Retrospective, case control	General practice	Prescription records	Statin use/cases 50 of 4719 Statin use/controls 318 of 15322* Adjusted for demographics, co-morbidities, prior vaccination, smoking, concurrent medications	0.49 (0.35–0.69)
Schlienger et al.; 1995–2002	Retrospective, nested case control	General practice	Computerized prescription database	Statin use/cases 141 of 1253 Statin use/controls 599 of 4838* Adjusted for demographics, co-morbidities, prior vaccination, smoking, concurrent medications	0.71 (0.56–0.89)
Myles et al.; 2001–2002	Population-based matched case control	General practice	Prescription records	Statin user/cases 178 of 3709 Statin use/controls 1050 of 22174* Adjusted for demographics, co-morbidities, smoking, concurrent medications	0.78 (0.65–0.94)
Dublin et al.; 2000–2003	Population-based case control	Integrated healthcare delivery system	Computerized pharmacy database	Statin use/cases 181 of 1125 Statin use/controls 327 of 2235* Adjusted for demographics, co-morbidities, prior vaccination, smoking, concurrent medications	1.26 (1.01–1.56)
Kwong et al.; 1996–2006	Retrospective cohort	Administrative healthcare databases	Prescription records	Statin use 1,120,319 No statin use 1,120,319 Adjusted for demographics, do-morbidities, concurrent medications	0.97 (0.94–1.00)
Smeeth et al.; 1995–2006	Population-based cohort	General practice	Computerized medical records	Statin use 129,288 Statin non-use 600,241 Adjusted for demographics, co-morbidities, concurrent medications, propensity matching	0.84 (0.74–0.95)
Fleming et al.; 1998–99 to 2005–2006	Population-based retrospective cohort	General practice	Electronic database; prescription records	Statin use 61,259 No statin use 267,622 Adjusted for demographics, co-morbidities, prior vaccination, smoking, concurrent medications	0.91 (0.73–1.13)
Vinogradova et al.; 1996–2005	Population-based nested case control	General practice	Prescription records	Pneumonia cases 17,755 Controls 80484* Adjusted for demographics, co-morbidities, prior vaccination, smoking, concurrent medications	0.78 (0.74–0.83)
Nielsen et al.; 1997–2009	Population-based case-control study	Healthcare databases	Prescription records from DNRP database	Statin use/cases 7223 Statin use/controls 64523* Adjusted for medications, comorbidities, recent surgery, socioeconomic indicators, influenza vaccination, and other markers of frailty or health awareness from medical databases	0.80 (0.77–0.83)
Novack et al.; 2003–2008	Secondary endpoint from JUPITER trail (RCT)	1315 sites in 26 different countries	Report from RCT	Rosuvastatin user/pneumonia cases 214 of 8901 Placebo user/pneumonia cases 257 of 8901 Adjusted for age, sex, smoking, presence of metabolic syndrome, lipid levels, and level of high-sensitivity C-reactive protein	0.83 (0.69–1.00)

Table 1 (continued)

Study; study period	Study design	Setting	Ascertainment of statin use	Cases/controls, n; confounders adjusted	Adjusted effect estimate
Lin et al.; 2000–2011	Retrospective, nested case control	Healthcare databases	Prescription claims from the NHIRD Taiwan	Pneumonia cases 2686 Controls 10726* Adjusted for CHASD2 score, medical conditions (diabetes mellitus, hypertension, chronic heart failure, stroke, COPD, chronic kidney disease, chronic liver disease, Parkinson disease, and dementia) and medication use and influenza or pneumococcal vaccine)	0.85(0.77–0.95)

*Matched cases and controls, (NHIRD) National Health Insurance Research Database, (DNRP) Danish National Registry of Patients, (RCT) Randomized controlled trail

objective evidence. The ascertainment of statin use was by way of administrative and pharmacy databases as a surrogate for statin use. In addition, because of the observational design of these studies, they were limited by both known and unknown confounders despite all adjustments done in the individual studies. Moreover, it has been suggested that the evidence may have been limited by the selective use of statins by populations who are more concerned for their health; the "healthy user bias" or conversely by a lack of use of statins by high-risk subgroups.

Given the paucity of robust, randomized evidence to assess statin use and the development of CAP conflicts over the results of the observational studies; the field currently depends on meta-analyses to shed light on the role of statins and take it forward. Keeping in mind the limitations of observational design of the studies and the interrogation of administrative databases, Khan et al. [5] conducted a meta-analysis to adjust both for known and unknown confounders by a novel approach. This approach sought to assess the presence of a hypothetical confounder and its characteristics to account for the desired outcome—the development of CAP. The meta-analysis demonstrated that the presence of the unknown confounder has to be severely imbalanced between the statin users and non-users to explain the reported associations. Moreover, other meta-analyses have reported on the topic and came to a similar conclusion [42, 43]. However, these meta-analyses are hypothesis generating and do not conclusively prove or disprove the association of the use of statins with the development of CAP.

Although, despite their limitations, most of the studies and their meta-analyses reported a protective effect of statins on the development of CAP, there is need both for biological studies to suggest the mechanism at play for the immunomodulatory role of statins and a well-designed and adequately powered RCT to conclusively demonstrate the clinical translation of the postulated biological role.

Conclusion

Taking into consideration the accumulated evidence to date, statins may have a role in the development and progression of CAP. The immune response to the infectious process may range from mild inflammatory response to severe sepsis. As witnessed with steroids, there may be a role for statins to attenuate the inflammatory cascade early during the response leading to beneficial outcomes. When the response becomes markedly dysregulated, statins lose their ability to play a meaningful role. However, the clinical importance of this postulated role is still unclear. It would be prohibitive to test this hypothesis in a general population as it may require a very large sample size. To be feasible, future RCTs can be designed

to test this in high-risk subgroups; elderly, immunocompromised, and patients with significant co-morbidities. Stratification based on immune status may also help to ascertain the role of statins to modulate the inflammatory response. With the current evidence, we are not in favor of initiation of statins either for the prevention or treatment of CAP.

Compliance with Ethical Standards

Conflict of Interest Drs Batais, Khan, and Abdulhak have no conflict of interests

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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