Réanimation (2013) 22:272-280
DOI 10.1007/s13546-013-0670-2

Statins and pneumonia: data from clinical studies

Statines et pneumonie : données issues d'études cliniques

D. Makris · E. Manoulakas · E. Papakrivou · E. Zakynthinos

Revised: 30 November 2012, Accepted: 19 February 2013

Abstract *Aim*: We reviewed the current literature in respect of the role of statin treatment as an adjunctive therapy in pneumonia.
Methods: Data for this review were identified through searches of PubMed and from bibliographies of relevant articles. The search was limited to publications in English and French.
Results: Statins present immunomodulatory properties. This has led to the hypothesis that statins might have the ability either to reduce the incidence of pneumonia or to improve the outcome of patients with pneumonia. Many observational retrospective and prospective studies have recently addressed this question. There is an increasing body of evidence suggesting that statins may be beneficial in pneumonia, although negative data have been also provided. However, data from randomized studies are very limited.
Conclusion: Treatment with statins may be beneficial in patients with pneumonia but data from large randomized studies are still needed to confirm it.

Keywords Statins · Pneumonia · VAP · Mechanical ventilation · Survival

Résumé *Objectif* : Nous avons étudié la littérature actuelle en ce qui concerne le rôle des statines, en tant que thérapie d'appoint dans la pneumonie.
Méthodes : Les données pour cette étude ont été identifiées grâce à une recherche sur PubMed d'articles pertinents. La recherche a été limitée aux publications en anglais et français.
Résultats : Les statines présentent des propriétés immunomodulatrices. Cette observation a conduit à l'hypothèse selon laquelle les statines pourraient avoir la capacité de diminuer l'incidence des pneumonies ou d'améliorer le pronostic des patients atteints de pneumonie. Plusieurs études observationnelles rétrospectives et prospectives ont récemment évalué cette question. Il y a un nombre croissant de preuves suggérant que les statines pourraient être bénéfiques dans la pneumonie, mais des résultats négatifs ont également été rapportés. Néanmoins, les données provenant d'études randomisées restent très limitées.
Conclusion : Les statines pourraient être bénéfiques pour les patients atteints de pneumonie, mais des données provenant d'études randomisées incluant un plus grand nombre de patients sont encore nécessaires pour confirmer ces observations.

Mots clés Statines · Pneumonie · PAV · Ventilation mécanique · Survie

Introduction

Pneumonia, community acquired (CAP) or hospital-acquired, is a common infection that is associated with increased morbidity and mortality [1–6]. This is especially true for severe forms of pneumonia that might be present in critically-ill patients like ventilator-associated pneumonia [VAP] [7]. Towards this direction, several strategies have been suggested to minimize the risk of developing pneumonia or to attenuate the burden of the disease [8].

Statins are inhibitors of HMG-CoA reductase which have the ability to regulate the synthesis of cholesterol. However, they also exhibit anti-inflammatory and immunomodulatory actions [9–13]. In this respect, it has been suggested that the pleiotropic characteristics of statins could be useful in the management of inflammatory diseases, including pneumonia [1–6,14–17]. Previous studies suggested that the use of statins may be associated with a reduced risk of fatal pneumonia and reduced mortality in patients with chronic obstructive pulmonary disease (COPD) and pneumonia related to influenza[2–4,14]. However, the relationship between the use of statins and the risk of developing or not pneumonia is not clear; it also remains elusive whether statin treatment can alter the course of pneumonia [5–6]. In the present report we review available evidence in respect of

D. Makris (✉) · E. Manoulakas · E. Papakrivou · E. Zakynthinos
University Hospital Larisa, Biopolis, Greece
e-mail : dimomakris@med.uth.gr

the role of statins as an adjunctive therapy in pneumonia and especially ventilator associated pneumonia.

Search Strategy and Selection Criteria

Data for this review were identified through searches of PubMed and from bibliographies of relevant articles. We undertook a comprehensive search in PubMed, through December 2012, using the terms "statins and pneumonia", "statins AND inflammation", "statins AND infection", "statins AND sepsis", "statins AND mortality without time limit. The search was limited to publications in English and French. In addition, we searched the online registry of randomized controlled trials of the US National Institutes of Health (http://www.clinicaltrials.gov) and the Current Controlled Trials website (http://www.controlled-trials.com) for ongoing investigations regarding this subject using the aforementioned terms. Eight hundred and sixty-four studies were initially found: 838 of them were excluded after abstract review either because they were irrelevant or, they were publications in the form of commentary. We focused on the remaining 29 clinical studies and metanalyses which assessed the effect of statins on the incidence or the clinical outcome of pneumonia.

Pleiotropic effects of Statin

There is now increasing evidence that statins present pleiotropic properties and their use could modify the inflammatory response [9–14]. These properties include down- or up-regulation of cytokines, modification of the function of leukocytes and lymphocytes, inhibition of Major Histocompatibility Complex II and reduction of cell injury markers such as caspases, apoptotic proteases [11,12,18].

Statins may block the synthesis of important intermediate products (isoprenoids) in the mevalonate pathway such as geranylgeranyl-pyrophosphate and farnesyl-pyrophosphate which regulates a variety of proteins such as guanosine triphosphate -binding proteins Ras and Rho [9], which are important for the inflammatory response. The inhibition of Ras and Rho isoprenylation by statins lead to accumulation of their inactive forms in the cytoplasm which in turn can activate peroxisome proliferative activated receptors (alpha, beta, delta, and gamma) that inhibitss the binding of transcription factor Nuclear Factor Kappa B to its DNA target sequence. On this basis, cytokine expression and production may be decreased.

Cytokine depression has been illustrated in airway epithelia cell models "treated" with statins. Iwata et al. [19] showed that Interleukin (IL)-6 and IL-8 mRNA expression and protein secretion in lipoplysaccharid (LPS)-stimulated cells were inhibited significantly by statins actions exerted via the mevalonic cascade and inhibition of Rho family in bronchial epithelial cells. The antinflammatory actions of statins have been also studied in animal lung infection models where animals were exposed to aerosolized LPS or intratracheal *Klebsiella pneumonia* [20]. It was found that statin treatment could reduce airspace neutrophils, parenchymal myeloperoxidases and microvascular permeability, and alter airspace and serum cytokines after LPS [20]. Similar antinflammatory actions have been recently demonstrated with the use of statins in animal models which were repetedly exposed in ambient particulate matter (PM10) air pollution [21,22]. PM10 can produce an acute pulmonary injury, characterized by an increase of inflammatory cells and cytokines in the lung [21]. PM10 have been shown to increase hospitalizations due to respiratory diseases in adults [23]. The exposure of aimals treated with statins to PM10 showed that statin downregulated the PM10-induced overactive bone marrow by attenuating the systemic inflammatory response [22]. As it was also shown by Ferraro et al. [21], acute intranasal exposure of animals treated with statins to ambient air particles prevented pulmonary cytotoxicity and inflammation.

Moreover, statins may present a favourable effect on oxidative stress. Statins may induce nitric oxide synthase (NOS) by reducing asymmetric dimethyl-arginine in lung epithelial cells– similar to their action in vascular endothelium [18]. On the other hand, it was shown that they may reduce nitrotyrosine in airway epithelium [18]. Thus, they present a double effect on airway epithelium by improving airway epithelial function and by attenuating oxidative stress. These actions of statins in the lung cells may affect the inflammatory burden during lung infection and might be useful in critical care patients with severe pneumonia, where the increased burden of inflammation may be detrimental [17,24].

Chow et al. provided evidence that statins present beneficial properties for bacterial killing and clearance [25,26]. In animal models where lung infection was induced by intratracheal administration of *Staphylococcus aureus*, the animals which were treated with statin presented enhanced bacterial killing and reduced systemic dissemination, elevated pro-fibrinolytic protein C levels, and reduced concentration of procoagulant tissue factor in lung lavage [25]. The same group reported other findings suggesting that statins may improve bacterial clearance [26]. They found that statin administration can favor the production of antibacterial DNA-based extracellular traps by human and murine neutrophils, monocytes/macrophages via the inhibition of the sterol pathway. Notably, this was evident although, paradoxically, both phagocytosis and oxidative burst were inhibited.

Those findings suggest that statin may be effective in lung bacterial infections via the promotion of enhanced bacterial clearance and of anti-coagulant activities. Certainly, one should also note that these favorable actions of statins do

not appear universally in the literature. Fessler et al. showed that native pulmonary clearance of *Klebsiella pneumoniae* was inhibited by statin and extrapulmonary dissemination enhanced both reversibly with mevalonic acid [20]. Therefore, clinical studies are necessary to assess whether the encouranging results in the basic level can be also useful in the everyday clinical practice.

The role of statins in reducing the incidence of pneumonia

Clinical studies which have addressed the question whether statins could have a prophylactical role in pneumonia are limitited (Table 1). Most of the findings come from retrospective analysis of data collected from large national registries, databases or post-hoc analysis of data from a randomized trial. A recent randomized trial with pravastatin provided interesting data that could form the basis for future trials [17].

In a large recently published study [27], data from the Danish National Registry were analyzed. Current use of statins was associated with a reduced risk for pneumonia [adjusted Odds ratio (OR), 95%-confidence interval (95% CI), 0.80 (0.77-0.83)] whereas the previous use of statins was associated with reduced risk but this association did not reach statistical significance [0.97(0.91-1.02)]. Similar results were also found when data form "The JUPITER"

Table 1 Clinical studies thathave investigated the impact of statin use on the risk for pneumonia

Type of pneumonia	Author	Type of Study	Setting	Number of cases	Risk of pneumonia
CAP	Vinogradova et al. 2011 (29)	Retrospective	General Practice database (QResearch database) (UK)	22.498	Adjusted only for comorbidities OR(95%CI) 0.81(0.76- 0.85) Adjusted for all confounding factors assessed in the study 0.78(0.74-0.83)
	Dublin et al. 2009 (31)	Retrospective	Healthcare delivery system (Group Health) services database (USA)	3.360	Adjusted OR(95%CI) 1.26 (1.01-1.56) -limited to pneumonia cases admitted to hospital 1.61(1.08-2.39)
Pneumonia	Nielsen et al. 2012 (27)	Retrospective	National Registry of Patients Data (Non-psychiatric hospitals, emergency departments, outpatient clinics) (Denmark)	70.953	Current use of statins: adjusted OR(95%CI) 0.80 (0.77-0.83) Previous use of statins: 0.97(0.91-1.02)
	Novack et al. 2012 (28)	Analysis of randomized clinical trial (The JUPITER) data	Multicentre-1315 centers (26 countries)	17.802	Adjusted HR(95% CI) 0.83(0.69–1.00) -before cardiovascular event: 0.81(0.67-0.97) -for recurrent event: 0.81 (0.67–0.98)
Pneumonia (diabetics)	Van de Garde et al. 2006 (30)	Retrospective	General Practice database (GPRD)-650 general practices (UK)	20.041	Adjusted OR(95%CI) 0.49(0.35-0.69)
VAP	Makris et al. 2011 (17)	Randomized Controlled Trial	Two-centre study ICU (Greece)	152	Thirty-day risk OR(95%CI) 0.55(0.27-1.13) ICU stay (mean 23 days) risk 0.54(0.27-1.10)

CAP: community-acquired pneumonia; CI: confidence interval; HR: hazards ratio; ICU: intensive care unit; OR: odds ratio; VAP: ventilator-associated pneumonia.

Table 2 Clinical studies that have investigated whether the use of statins improve outcomes in pneumonia

Type of disease	Author	Type of Study	Setting	Number of cases	Outcome
CAP (cases with AKI)	Murugan et al. 2012 [34]	Prospective	Multicenter study – twenty teaching and non teaching hospitals (USA)	631	One-year mortality adjusted OR(95%CI), 0.72(0.50-1.06)
CAP	Chalmers et al.2008 [32]	Prospective	One centre - university hospital (UK)	1007	Thirty-day mortality adjusted OR(95%CI) 0.46(0.25 - 0.85)
	Majumdar et al.2006 [5]	Prospective	Multicenter- six hospitals (Canada)	3415	Mortality or ICU admission adjusted OR(95% CI) 1.10(0.76-1.6)
	Mortensen et al.2008 [33]	Retrospective	Veterans Affairs Administrative Database (USA)	8.652	Decreased hospital mortality adjusted OR(95%CI) 0.54(0.42-0.70)
	Mortensen et al.2005 [2]	Retrospective	Two centre study – teaching hospitals (UK)	787	Thirty-day mortality OR(95%CI) 0.36(0.14-0.92)
	Chopra et al. 2012 [41]	Metanalysis Thirteen prospective retrospective studies	General and Teaching hospitals, Acute Care Facilities, General practice registration Data base	254.950	Mortality overall, adjusted OR(95% CI) 0.66(0.55-0.79) - in retrospective studies 0.65(0.53-0.81) - in prospective studies 0.73(0.48-1.10) Thirty-day mortality 0.48(0.39-0.59) Inhospital mortality 0.90(0.82-0.98) Six-month mortality 0.67(0.41-0.91)
Pneumonia/ influenza	Frost et al. 2007 [4]	Retrospective	Health Organizations Registry (Lovelace Database) (USA)	76.239	Mortality adjusted HR (95% CI) 0.61(0.41-0.92)
Pneumonia/ Influenza A (H1N1)	Viasus et al.2011 [35]	Prospective observational	Multicentre – thirteen tertiary hospitals (Spain)	197	Development of severe disease adjusted OR(95%CI) 0.64(0.22-1.86) (the use of statins was assessed both alone and in a group with corticosteroids, macrolides)
Pneumonia	Mortensen et al.2012 [36]	Retrospective	Veterans Affairs Administrative Database (USA)	22.996	Mortality for prior statin users OR(95%CI), 0.74(0.68-0.82) Mortality for inpatients statin users 0.68(0.59-0.78) Mechanical ventilation for prior statin users 0.81(0.70-0.94) Mechanical ventilation for inpatients statin users 0.68(0.60-0.90)

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Table 2 *(suite)*

Type of disease	Author	Type of Study	Setting	Number of cases	Outcome
	Nielsen et al. 2012 [27]	Retrospective	Danish National Health Service Database (Denmark)	70.953	Thirty-day mortality adjusted HR(95%CI) 0.73(0.67-0.79)
	Rothberg et al.2012 [40]	Retrospective	Administrative database (376 hospitals) (USA)	121.254	Inhospital mortality adjusted OR(95% CI) 0.86(0.79-0.93) - for ICU patients 0.93(0.81-1.06), - outside ICU 0.79 (0.71-0.87).
	Douglas et al. 2011 [39]	Retrospective	Health Improvement Network database (UK)	9.073	Six-month mortality adjusted OR(95%CI) 0.67 (0.49-0.87)
	Myles et al. 2009 [37]	Retrospective	General Practice Data Records (The health improvement network) (UK)	3.681	Thirty-day mortality for current statin users adjusted HR(95%CI) 0.33(0.19-0.58) long-term mortality, adjusted HR(95%CI) 0.45(0.32-0.62)
	Dublin et al. 2009 [31]				
	Thomsen et al. 2008 [38]	Retrospective	The Danish National Health Service Data (Denmark)	29.900	Thirty-day mortality OR(95%CI) 0.63(0.54-0.75) Three-month mortality 0.72(0.63-0.82)
	Schlienger et al.2007 [3]	Retrospective	General Practice Research Database (UK)	6.091	Mortality due to pneumonia OR (95%CI) 0.47(0.25 - 0.88)
	Ma et al. 2012 [42]	Metanalysis Sixteen prospective retrospective studies and of one rando-mized study	General and Teaching hospitals, Acute Care Facilities, Local Health Data Libraries, National Registration Libraries	≈240.000	Mortality adjusted OR(95% CI) 0.69(0.62-0.78)
VAP	Makris et al. 2011 [17]	Randomized control trial (pravastatin for 30 days)	Two-centre -ICU (Greece)	152	Thirty-day mortality OR(95%CI) 0.37(0.13-1.01) ICU mortality 0.38(0.17-0.88) Six-month mortality 0.99(0.51-1.91)

AKI: acute kidney injury; CAP: community-acquired pneumonia; CI: confidence interval; HR: Hazards ratio; ICU: intensive care unit; OR: odds ratio; VAP: ventilator-associated pneumonia.

trial [28] were analyzed and the use of statins was associated with reduced hazards ratio (95%CI) for pneumonia before a cardiovascular event 0.81(0.67-0.97), and statins were found to act prophilactically for recurrent pneumonia events [0.81 (0.67–0.98)].

With respect to CAP two recent large studies [29,30] that included data from the general practice registries pointed also out that statins could reduce the risk for pneumonia. On the other hand, Dublin et al. [31] did not find an association between the previous use of statin and the risk for pneumonia among immunocompetent, community dwelling older people.

A randomized trial assessed whether statin treatment can reduce VAP incidence. The use of a 30-day regime with statins in critical care patients without previous use of statins (previous use of statins was determined as an exclusion criterion from the study) has not significantly modified the risk for VAP. However, we should note that there was a trend toward a higher probability of being free from VAP during the 30-day treatment period in the statin arm compared to controls ($p = 0.11$) in Kaplan-Meier survival analysis. When data were stratified according to the median APACHE score, it was found that patients who were treated with statins with APACHE score ≥ 15 had marginally increased probability of being free of VAP compared to controls during the 30-day treatment period ($p = 0.06$), and significantly increased probability during the whole intensive care uni (ICU) period ($p = 0.04$) [17].

The role of statins in improving the outcome of patients with pneumonia

The number of clinical studies which investigated the ability of statins to improve outcomes in pneumonia cases is larger compared to studies that investigated the impact of statins on the incidence of pneumonia (Table 2).

In respect of CAP, Chalmers et al. [32] found in a prospective observational study of patients admitted with CAP that the use of statins was significantly associated with decrease risk of thirty-day mortality adjusted OR (95%CI) of 0.46 (0.25–0.85) and development of complicated pneumonia [0.44(0.25–0.79)]. Mortensen et al., in a retrospective analysis of two-centre data found that the use of statins was significantly related with a decreased 30-day mortality rate [2]. The study included approximately 800 patients with a radiographically confirmed infiltrate or other findings consistent with CAP on chest radiography or computed tomography scan, including 110 subjects (14%) taking statins at presentation. The use of statins at presentation was associated with a decreased 30-day mortality rate OR (95% CI) 0.36 (0.14–0.92), using multivariate regression analysis; mortality was adjusted for several potential confounders including a propensity score. Mortensen et al. [33] confirmed these results in a larger retrospective study where statins were found to be associated with decreased risk of hospital mortality OR (95% CI) of 0.54 (0.42-0.70).

However, a large prospective study came to a different conclusion [5]. The authors included 3415 patients hospitalized with CAP where 10% of the population was receiving a statin before admission. The statin use was associated with a lower risk to die or be admitted to an ICU (OR 0.80, $p = 0.15$). However, when age and propensity score were also taken into account in multivariate regression analysis, the results shifted to a potentially harmful effect of statins with an odds ratio (95% CI) of 1.10 (0.76-1.60). Similarly, Murugan et al. in a multicentre prospective study in patients hospitalized with CAP found that statin use was associated with a lower risk for death at one year (27.8% versus 38.8%; $p = 0.01$) [34]. However, no significant effect was found after adjustment for differences in age, severity of pneumonia and acute kindney injury, use of mechanical ventilation, and propensity score.

In pneumonia cases associated with influenza infection data are limited. Frost et al. found a beneficial effect of statins in mortality adjusted hazards ratio (95% CI) 0.61 (0.41-0.92) in a retrospective study [4]. In contrast, prospectively collected data from Viasus et al. did not confirm this relationship [35]. However, we should clarify here that the authors assessed the impact of immunomodulatory treatment including corticosteroids, macrolides and statins. In addition, the number of patients who received statins in the study was only 12 out of 197 (6%) patients [35]. Thus, definitive conclusion cannot be drawn for this particular category of pneumonia cases.

Large cohort studies which were based on data retrieved from large national databases [27,36–39] suggest that the use of statins can be beneficial either when thirty-day mortality [27,38], three month-mortality [38], six-month mortality [3,39] or inhospital mortality [40] was assessed. A study that could well illustrate the relationship between statins and survival in pneumonia patients is the one reported by Schlienger et al. [3]. They matched patients with pneumonia with control subjects based on age, sex, general practice, and index date. After adjusting for co-morbidity and frequency of visits to general practitioners, current statin users were found to have a significantly reduced risk of fatal pneumonia [adjusted OR (95% CI), 0.47(0.25–0.88)] and reduced - but not statistically significant- risks of uncomplicated pneumonia, and pneumonia associated hospitalization. Notably, fibrate use at any time, was not associated with reduced risk of pneumonia and thus, one might argue that the beneficial effects of statins on pneumonia were linked to their specific properties and do not result from the lipid-lowering effect of the drug.

The effect of treatment with statins in VAP was assessed in a two-centre randomized trial in critical care patients [17]. The probability of survival during the 30-day treatment period and during the whole ICU stay was marginally increased in patients who received statin compared to controls ($p = 0.07$). When data were stratified according to median APACHE score, it was found that patients treated with statin with APACHE score ≥ 15 had significantly increased probability of survival compared to controls, during the 30-day treatment period ($p = 0.04$) and marginally increased probability during the whole ICU period ($p = 0.06$). The authors suggested that the beneficial effect of statins might be explained by potential "antiinflammatory" or "anti-infectious" capability of statins which may reduce the inflammatory burden of the most severe forms of critical illness.

In reviews and metanalysis of published studies in CAP, the use of statins seems to be associated with positive outcomes [1,41,42]. Chopra et al [41] in a metanalysis of thirteen prospective and retrospective studies found that mortality was overall reduced [adjusted OR (95% CI), 0.66 (0.55–0.79)]. This association was also evident when data were analysed according to thirty-day, six-month and inhospital mortality. However, we should also note that the authors found that the positive relationship between statins and survival was more evident in metanalysis of data of retrospective studies; the risk of death in prospective studies was not significantly reduced [0.73 (0.48–1.10)]. In another metanalysis [42] of sixteen prospective and retrospective studies regarding pneumonia studies - not only CAP – statins was also associated with reduced risk of mortality [OR (95% CI), 0.69 (0.62–0.78)].

Discussion

Many studies have demonstrated that statins present pleiotropic properties and their use could modify the inflammatory response [9–13]. Therefore, statins may inhibit the progression of septic conditions by modifying the inflammatory cascade. Notably, several recent studies have demonstrated that the use of statins may be associated with a favourable outcome of inflammatory diseases such as bacteremia, sepsis, multiple organ dysfunction syndrome, and pneumonia [1–6,14–17]. In this respect, the potential use of statins in the clinical setting of those critical clinical conditions attracts interest and it has been suggested that they might have a role in the management of severe infections [43]. In the present review we found that a) an increasing number of clinical studies suggest that statins may have a beneficial role in the outcome of pneumonia, b) data regarding the role of statins in reducing the frequency of pneumonia among subjects are limited and c) there is a lack of randomized studies that could address adequately these issues.

The beneficial effects of statins in the setting of infection have been demonstrated in many clinical investigations. However, most of them were observational studies with either retrospective or prospective design [2,14,44]. In this respect, one might argue that results may be biased by several factors which have to be underlined and may limit the enthusiasm for the beneficial effects of statins in severely infected patients. Most studies which investigated the role of statins on infections included cardiovascular patients in the branch of statins [2,14,44]. As it might be expected, the patients receiving statin therapy were more likely to be older or to have more comorbidities from non-statin group, with multiple differences in baseline characteristics. The level of the Charlson Index score, a measure of comorbidities which was used in two studies [4,45], was higher in patients receiving statins; in particular it was medium to high in 84% of the statin users, compared with only 66% of the nonusers [46]. Patients in the statin group had more chronic diseases, as evidenced by significantly higher rates of hypertension, chronic ischemic heart disease, cerebro-vascular disease, diabetes, chronic renal failure, as well as higher levels of total cholesterol and triglycerides. In this respect, results favouring the use of statins might have been amplified by the fact that patients receiving statin therapy had more co-morbidities [2,4,44]. In addition, one could argue that these patients may have received more attentive care due to their multiple co-morbidities and thus had better outcomes. Statins is a preventive therapy for cholesterol control; outpatients who initiate such a therapy may also adhere to other health behaviours that may decrease the risk of adverse outcomes.

Another point that should be underlined is the lack of information regarding the appropriate antibiotic therapy in previous studies that included patients with pneumonia [4,30] or even more lack of information regarding overall treatment in patients with severe septic diseases [30,47,48]. In one study for example [44], it is unclear how many of the patients already had severe sepsis at presentation. In this case, the proposed benefit of statin therapy may be blunted. These limitations of retrospectively designed studies may have affected results by several confounders that have not been included in the analysis and should be considered in the interpretation of results regarding the effect of statins in patients with infection.

However, there are other studies [4,39,49] where adjustment for several confounders (sex, age, smoking pulmonary function and co-morbidities) were made and the hazard ratio for statin users was significantly lower compared to nonusers. This should be also underlined.

Randomized controlled prospective trials could provide a better insight regarding the role of statins in infectious

diseases and pneumonia. These studies should ideally incorporate double blind design (placebo vs statins) or at least, double placebo control open label design to investigate adequately the effect of prophylactic use of statins in morbidity and mortality of patients with pneumonia in the critical care setting. However, data from such studies are for the time being very limited.

The findings of the above discussed randomized controlled study [17] are encouraging suggesting that statins may be useful as an adjunctive therapy in critical ill patients. However, as it has been pointed out [50] this was a relatively small randomized study that was not sufficiently powered (in other words the probability to find a significant effect of pravastatin if it exists, was low). Furthermore, due to the sparity of evidence, it may be difficult to assess safety issues in the critical care setting and the results of Makris et al. [17] should be interpreted wisely. Thus, the question remains. However, the results of that study [17] provides encouragement for new, larger randomized studies in patients with severe critical ilness to investigate the effect of statins on nosocomial infections and outcomes in the ICU.

Another point that should be underlined here is the safety of using statins in the critical care setting. Patients with sepsis and pneumonia might be in acute or acute on chronic organ failure and pharmacokinetics of statins may become complex. Concerns have been raised about the adverse effects of statins due to increases in creatine kinase, myopathy and rhabdomyolysis that have been reported [43]. On the other hand serious events (creatine phosphokinase > 10 times of normal or rhabdomyolysis) are infrequent. Many authors suggested that statins are generally well tolerated and have generally a good safety profile [2,5,14,43]. Two usual side-effects of statins, such as liver dysfunction and myositis, are very common complications of sepsis, and therefore, these adverse effects might be overestimated in former studies which included patients with sepsis. In an aforementioned study performed in critically ill patients [17], pravastatin treatment was not associated with adverse events in the ICU. Nevertheless, bearing in mind potential side effects of statins like rhabdomyolysis, future studies should investigate the pharmacokinetics of statins in these patients and whether some statins are more advantageous due to their specific pharmacokinetic properties and/or due to the pharmacodynamic results.

Conclusion

The use of statins may have beneficial effects in the incidence, the course and the outcome of pneumonia. Furthermore, recent findings suggest that pravastatin treatment in the ICU is safe and it might have a beneficial role in the frequency and outcome of VAP, especially in patients with more severe illness. However, despite these encouraging data, evidence is limited mainly in observational studies and there is a lack of large randomized studies in this field. Thus, whether statins should be administered in pneumonia as an adjunctive therapy after the onset of acute illness or chronically for being effective is still an open though interesting question.

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