Statins and pneumonia: data from clinical studies

Statines et pneumonie : données issues d’études cliniques

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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
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 metaanalyses 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 inhibits 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 lipopolysaccharid (LPS)-stimulated cells were inhibited significantly by statins actions exerted via the mevalonic cascade and inhibition of Rho family in bronchial epithelial cells. The antiinflammatory 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 antiinflammatory actions have been recently demonstrated with the use of statins in animal models which were repeatedly 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 animals treated with statins to PM10 showed that statin down-regulated 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