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THE EFFECTS OF STATIN THERAPY ON PNEUMONIA OUTCOMES

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HMG-CoA reductase inhibitors (statins) are the most prescribed class of drugs in the world. Some authors suggest that positive effects of statins were reported for statins against pneumonia. These positive studies data were counterbalanced by at least one negative prospective cohort study. Where lies the truth? Better understanding the statins influence and their potential role in pathophysiological pneumonia mechanisms is needed because of high quantity of subjects receiving statins with numerous medical conditions significantly associated with increased short-term mortality.

KEY WORDS: statins, pneumonia, outcomes, statin effects

ВПЛИВ ТЕРАПІЇ СТАТИНАМИ НА РЕЗУЛЬТАТИ ЛІКУВАННЯ ПНЕВМОНІЇ

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Інгібітори ГМГ-КоА-редуктази (статини) є класом медикаментів, що призначається найчастіше у світі. Деякі автори в публікаціях відзначають позитивні ефекти терапії статинами у разі захворювання пневмонія. Позитивні дані цих досліджень були врівноважені, принаймні одним негативним результатом у ході проспективного когортного дослідження. Де знаходиться істина? Краще розуміння впливу терапії статинами і їх потенційної ролі в патофізіологічних механізмах захворювання пневмонія необхідно через високу кількість суб'єктів, які отримують статини, з численними захворюваннями, пов'язаними з підвищеною короткостроковій смертності.

КЛЮЧОВІ СЛОВА: статини, пневмонія, результати, ефекти статинів

ВЛИЯНИЕ ТЕРАПИИ СТАТИНАМИ НА ИСХОДЫ ПНЕВМОНИИ

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Ингибиторы ГМГ-КоА-редуктазы (статины) наиболее часто назначаемый класс медикаментов в мире. Некоторые авторы в публикациях отмечают положительные эффекты терапии статинами в случае заболевания пневмония. Позитивные данные этих исследований были уравновешены, по крайней мере одним отрицательным результатом в ходе проспективного когортного исследования. Где находится истина? Лучшее понимание влияния терапии статинами и их потенциальной роли в патофизиологических механизмах заболевания пневмония необходимо из-за высокого количества субъектов, получающих статины с многочисленными заболеваниями, связанными с повышенной краткосрочной смертности.

КЛЮЧЕВЫЕ СЛОВА: статины, пневмония, результаты, эффекты статинов

HMG-CoA reductase inhibitors (statins) are the most prescribed class of drugs in the world as a common chronic treatment because they significantly improve survival in patients with cardiovascular disease and in apparently healthy persons without hyperlipidemia but with elevated C-reactive protein levels [1]. Besides this well-known effect, they are responsible in decreasing of intermediary products of mevalonate synthesis cascade inhibition, including farnesyl pyrophosphate and geranyl

pyrophosphate, which are involved in the activation by isoprenylation of small GTP-binding proteins, which are involved in the pleiotropic effects of statins. These actions result in numerous effects of statins as anti-inflammatory and anti-oxidant, immune modulation, antithrombotic effects, protection of the endothelial function, and activation of vitamin D, decrease in the activity of platelets, an increase in the tissue plasminogen activator and a decrease of its inhibitor, and an enhancement in the expression and functional activity of thrombomodulin, an essential co-factor for protein C activation [2]. The inhibition of mevalonate synthesis by statins leads to a lesser activation of the small GTP-binding proteins, which play a key role in the activation (molecular on/off switches) of intracellular inflammatory signaling pathways. In particular, the activation of nuclear factor kappa B, mitogen-activated protein kinase, and phosphatidylinositol-3 kinase systems by isoprenylated protein kinases is blunted. Therefore, the expression of cytokines, acute phase proteins, chemokines, adhesion molecules, and enzymes is partially inhibited in the presence of statins [3]. For example, the JUPITER study showed that rosuvastatin significantly lowers CRP levels, an independent predictor of future cardiovascular events [4, 5]. Statins influence leucocyte function by a direct inhibition of the major histocompatibility complex type II gene of antigen presenter cells and an allosteric block site of the lymphocyte function-associated antigen [6], which has a significant role in lymphocyte adhesion and activation.

Are statins antibacterials? Japanese microbiologist Akira Endo was first who discovered in the 1970s, during a research for antimicrobial agents, natural products with a powerful inhibitory effect on HMG-CoA reductase in a fermentation broth of Penicillium citrinum, including ML236B (compactin). In spite of this no useful antimicrobial activity has been found in case of HMG-CoA reductase inhibitor previously [7, 8]. Clinical trials data with compactin have never been made public believed due to his serious animal toxicity, that`s why lovastatin became the first public known HMG-CoA reductase inhibitor with clinical studies data [9]. Lovastatin in animal and in vitro studies showed inhibition of the bacterial growth of strict intracellular bacteria such as Coxiella burnetii [10]. Researchers believed that it became possible because the genome of these bacteria contains the steroid biosynthesis pathway, and bacterial multiplication is achieved in a vacuole rich in cholesterol [11]. Nowadays, according to a meta-analysis of a number of observational studies patients on statin therapy seemed to have a better outcome of bacterial infections in respiratory tract infection, but the association did not reach statistical significance after adjustment for apparent publication bias OR 0.79 (95 % CI 0.58–1.07). 12 from 15 observational studies on pneumonia and statins, showed association between statin-use and a favorable outcome [12]. In another study, patients, which are receiving statins for prolonged periods also as older patients, may have a higher plasma simvastatin levels compared with healthy volunteers. Some statins, in particular simvastatin, had an antimicrobial effect in vitro but require concentrations that are far higher than are probably achieved in vivo with traditional indications for statins. In this study simvastatin showed an unexpected significant antimicrobial effect against MSSA (Methicillin-sensitive Staphylococcus aureus) (mean MIC 29.2 mg/L) and to a lesser extent against MRSA Methicillin-resistant Staphylococcus aureus) (mean MIC 74.9 mg/L) on bacterial growth and to assess possible synergistic effects with penicillin. The aim of another similar study was determined MIC-values with possible antibacterial effects for simvastatin, fluvastatin and pravastatin against primary pathogens of the respiratory tract (S. pneumoniae, M. catarrhalis and H. influenza) by traditional antibacterial assays. Low Simvastatin concentrations that was detected in human blood during therapy (1–15 nmol/L) and just a single doses of statins was given to healthy volunteers, can explain the fact that improving of antibacterial effects of whole blood was not detected. Contrariwise, as in above mentioned investigations was found that simvastatin at high concentrations 15 μg/mL (36 μmol/L) rapidly kills S. pneumoniae and M. catarrhalis. Statins did not affect growth or viability of H. influenzae. Thus, according to the results of the study, a direct bactericidal

effect of statins in vivo is probably not the mechanism which can explain beneficial effect of statins against various infections [13]. Earlier observed beneficial effect of statins might be explained by potential anti-inflammatory properties [14], also, statins have been reported to inhibit host cell invasion by Staphylococcus aureus [15] as well as to enhance bacterial clearance of this pathogen [16] and also has been proposed a direct antibacterial effect against it [17 - 18]. Recently, statins were shown not only to improve killing of Staphylococcus aureus by phagocytic cells [19]. All in vitro experiments mentioned above have been performed using statin concentrations between 0.1–50 μM, which greatly exceeds the concentrations present in human blood during statin treatment (1–15 nmol/L) [20, 21]. Statin concentrations in these cell experiments were compared with concentrations detected in human plasma.

Positive antimicrobial effect of statins was found not only in case of respiratory pathogens but also in case of periodontal pathogens that have been identified in atheromatous tissue and associated with increased carotid intima media thickness. The main periodontal pathogen. Porphyromanos gingivalis, seem to increases the number of macrophages, T-cells and lipids within the plaques. Increased levels of inflammatory biomarkers such as C-reactive protein (CRP) were found to be predictive of acute events in healthy individuals. Hyperlipidaemic patients were found to be more prone to periodontitis, and statins can be beneficial for periodontal health [22]. Moreover, statins have been shown to protect against pneumococcal infection in a mouse model of sickle cell disease [18] and in vitro to inhibit a number of strains of fungi and the parasite Plasmodium falciparum, but statins concentrations in these experiments were much higher than in serum during statin therapy. Murine models have shown also anti-chlamydial and immunomodulatory effects of simvastatin during infection [23]. Another study showed the antibacterial effect of atorvastatin and rosuvastatin in Gram + and Gram–bacteria [24]. Result of other studies suggest the superiority of the antibacterial effects of atorvastatin or simvastatin to that of rosuvastatin. MSSA, MRSA, vancomycin-susceptible enterococci (VSE), vancomycin-resistant enterococcus (VRE), acinetobacter baumannii, staphylococcus epidermidis, and enterobacter aerogenes, were more sensitive to both atorvastatin, and simvastatin compared to rosuvastatin. On the other hand, escherichia coli, proteus mirabilis, and enterobacter cloacae were more sensitive to atorvastatin compared to both simvastatin and rosuvastatin [25]. Systematic review and meta-analysis of Imad M. Tleyjeh et. (2009), suggest that statin use may be associated with a beneficial effect in treating and preventing different infections. Patients who have infections and are taking statins had a better outcome, including chance of survival: adjusted effect in treating infections was 0.55 (95 % confidence interval, 0.36–0.83; I2 = 76.5 %) in favor of statins. The pooled effect estimate addressed infection prevention was 0.57 (95 % confidence interval, 0.43-0.75; I2 = 82 %) in favor of statin use [26].

Among possible mechanisms of antimicrobial activity can be sort out interference with L-mevalonic acid synthesis, COX-2 modulation, reactive oxygen species suppression. Statins have been shown to lower LDL levels by interfering with mevalonate synthesis with influence pathogen-induced inflammation. Increased COX-2 stability by Atorvastatin, could increase dendritic cell function after infectious bouts with compensation of some adverse effects of sustained inhibition of COX-2. On the other hand, possible involving reduced formation of reactive oxygen species, oxidation of LDL and adhesion of neutrophils, while apoptosis, bacterial phagocytosis and bacterial clearance are unaffected in case of Simvastatin allows to have a protective role in lung inflammation [27]. Experimental studies have shown their effect in the modulation of the cytokine cascade and in the organization of the immunological response to respiratory infection [28]. For example, statin therapy was associated with a reduction in the levels of inflammatory cytokines in patients with acute bacterial infections: TNF-α and IL-6 levels were significantly reduced in the simvastatin group ($p = 0.02$ and $p = 0.02$, respectively), while no such difference was observed in the placebo group [29]. Although it has been

suggested that statins may have an effect in the modulation of the cytokine cascade and on the prognosis of patients with community acquired pneumonia (CAP). However, prospective, randomised, double–blind, placebo–controlled trial data showed that use of simvastatin, 20 mg once daily for 4 days, since hospital admission did not reduce the time to clinical stability and the levels of inflammatory cytokines in hospitalised patients with community-acquired pneumonia [30].

During of the role of statins in community acquired pneumonia, [31] was shown that statins have immunomodulatory, and antioxidative actions, and a significant effect on the concentrations systemic cytokine [23-26]. Linnea A. Polgreen etc. reports data showed that the protective effect of statins against pneumonia among 19,078 (15.3 %) patients that were diagnosed, after surviving for 1 year post- acute myocardial infarction, is most likely the result of non-random treatment assignment (i.e., a healthy-user bias). The statin coefficient -0.016 ($p < 0.001$), indicated that statins therapy was associated with a reduction in pneumonia rate in this category of patients [32]. There have been other three retrospective studies also showed improved outcome in patients taking statins. It was found than statin use is independently protective against increasing of C-reactive protein levels, the value of which failed to decrease by 50 % or more at day 4 (AOR 0.52, 95 % CI: 0.30-0.89, $p = 0.02$). Also in these studies, statins reduced cytokine and other inflammatory markers levels in patients with cardio-vascular pathology, and it was predisposed that the improved outcome in patients with pneumonia happened due to the anti-inflammatory and immunomodulatory effects of the statins. [33]. Other studies showed in-vitro that simvastatin therapy (1μM) can cause restoring of neutrophil migration (preserved chemokinesis) and old neutrophil chemotaxis (directed migration) in patients with pneumonia to baseline values despite the patients older age compared with healthy controls (pneumonia, 1·1 μm/min, $p = 0·02$). 2 weeks of oral simvastatin in healthy volunteers over ≥ 65 years, ($n = 20$) increased the accuracy of neutrophil migration in vitro (MD 1·68 μm/min, $p = 0·02$) replicating in-vitro work. [34]. As prophylaxis or in the very early management, the anti-inflammatory effects of statins may be protective in sepsis, but side effects may prevail as the disease progress with establishing of multiorgan dysfunction. Supratherapeutic plasma levels of statins and their hepatic metabolization in critically ill patients can be translated to an increasing the risk of toxicity. Also metabolization of statins by the cytochrome P450 3A4 system may interfere with other medications commonly used in the Intensive Care Unit (ICU) (i.e., amiodarone, macrolide anti-biotics) [2]. Prior studies suggested a potential survival benefit for statins in severe infections, from patients already receiving the lipid-lowering therapy. E.M. Mortensen etc. [35] found that prior outpatient use of statins was strongly associated with a decreased 30-day mortality for subjects aged over 65 years that were hospitalized with CAP diagnosis and increasing incidence of pneumonia and pneumonia-related mortality. In total, were included 8,652 subjects, among them 18.1 % of subjects were using statins. Adjusting of potential confounders showed, that current statin use (odds ratio (OR) 0.54, 95 % confidence interval (CI) 0.42–0.70) were significantly associated with decreased 30-day mortality. In another large cohort study was found that preadmission statin use was associated with considerably reduced risk of death among ICU patients. The reduced risk of death remained robust in various subgroup analyses, including among new and long-term statin users, no clear association wasn't found between former statin use and non-statin lipid-lowering drug use and risk of death, which supports a causal association between statin use and reduced risk of death among ICU patients [36]. In a 2006 Schmidt and colleagues reported results of German cohort study with 120 ICU patients with multiple organ dysfunction syndrome included, where statin use was associated with substantially reduced in-hospital mortality (MRR = 0.53, 95 % CI = 0.29 to 0.99) [37]. The biological mechanisms underlying this data are not entirely understood still. Some authors decided that strong experimental evidence of beneficial statins effects on platelet function, coagulation, fibrinolysis, plaque formation, and inhibition of endothelial dysfunction [38-43] can decrease the risk of fatal venous

and arterial thrombotic events due to presence of systemic inflammatory response syndrome and/or severe infections in ICU patients [44-46]. Multi-analysis of fourteen studies with 269,739 participants included showed that statin treatment was associated with lower 30-day mortality, with an OR of 0.44 (95 % CI, 0.29-0.67), and an adjusted OR of 0.59 (95 % CI 0.48-0.73, NNT30d = 19). Statin therapy was also associated with lower long-term (> 30 days) mortality, with an OR of 0.49 (95 % CI, 0.29-0.84) and an adjusted OR of 0.65 (95 % CI, 0.51-0.82, NNTlong-term = 15) [47].

These positive studies data need to be counterbalanced by at least one negative prospective cohort study of admitted for treatment of suspected or confirmed infection to hospital wards patients, where the risk of significant clinical deterioration was low, with a 30-day mortality of 5.7 % and ICU admission risk of 3.3 %. Markers of systemic inflammation (CRP, WCC) improved with time but prior statin therapy did not alter the evolution of these inflammatory markers levels. [48]. Sachin Yende et all. [49] in a large, prospective, multicenter cohort study of patients hospitalized with CAP, found no evidence of a protective statins effect on the development of severe sepsis. In this study authors made not only comparison of statins use (in the week before admission) and with no prior use patients groups but also they compared prior statin users with continued inhospital therapy (continued use cohort) with no prior use or no inhospital use group. Were found only modest differences in levels of circulating biomarkers in community-acquired pneumonia, perhaps due to healthy user effects and indication bias. Adjustment of patient's characteristics and propensity for statin use, showed no mortality benefit in prior (odds ratio, 0.90 [0.63–1.29]; p = 0.57) or continued statin use groups (odds ratio, 0.73 [0.47–1.13]; p = 0.15). Further investigations showed that adding a statin to antibiotic therapy didn't lead to survival improvement in critically ill patients with ventilator-associated pneumonia (VAP). Investigation data helped to emphasize that 28-day mortality was higher in case with simvastatin - 22.6 % (95 % confidence interval [CI], 15.7 % - 31.5 %) compared with placebo group - 14.3 % (95 % CI, 8.9 % - 22.2 %, P = 0.06); between-group difference, 8.3 % [95 % CI, − 2.2 % to 18.7 %]). This trial was stopped early for futility underscores that statins should not be employed as adjunctive therapy [50]. Prospective population based cohort study of CAP patients managed in an outpatient setting, was made from 2000–2002, showed that have shown either no association with mortality or increased mortality with the use of these medications in subjects with infectious diseases [51-52]. Meta-analysis of observational studies such as cohort studies and case-control studies of pneumonia inpatients, identified that in this case the raw data demonstrated no significant benefit from statin therapy (OR = 0.86, 95 % CI, 0.56-1.34) [53]. In the Dublin study, statin use appeared to predispose to, rather than protect against pneumonia. In the minimally adjusted model, statin use had a odds ratio of 1.13 (0.95–1.34), while in the fully adjusted model statin use had a odds ratio of 1.26 (1.01–1.56). In 2006 was made big prospectively collected database study on 3415 patients in 6 hospitals observed that confounding due to the "healthy user effect" may be responsible for the observed benefits of statins. No significant association was found, the theory that patients taking statins are also more likely to do other beneficial health behaviors such as taking pneumococcal and influenza vaccination or stopping smoking that may be associated with better outcome [54].

Why have other authors failed to demonstrate a benefit for statins therapy if the previous some studies have shown it? Some authors suggest that positive effects of statins were reported for statins against pneumonia due to the differences in patients group who were treated with statins and those who were not. The biggest part of reports about protective effects of statins against pneumonia and other infections was based on data where treatments are not assigned randomly. In other cases it was maybe the small amount of patients included in the study. Also the result can be affected by the severity of concomitant pathology, personal experience of the patient, administration by family doctor or self-administration of antibiotics drugs before the admission to the department, influence of other medications taken for chronic disease

etc. Better understanding the statins influence and their potential role in pathophysiological CAP mechanisms is the need to since subjects receiving statins have numerous medical conditions significantly associated with increased short-term mortality.

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