Title

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Journal

Current Medical Research and Opinion, 30(6)

ISSN

0300-7995

Author

Zeki, Amir A

Publication Date

2014-06-01

DOI

10.1185/03007995.2014.881794

Peer reviewed

HHS Public Access

Author manuscript

Curr Med Res Opin. Author manuscript; available in PMC 2018 June 27.

Published in final edited form as:

Curr Med Res Opin. 2014 June ; 30(6): 1051–1054. doi:10.1185/03007995.2014.881794.

Statins and asthma: where we stand, and the next critical steps in research

Amir A. Zeki

University of California, Davis, Sacramento, CA, USA

Abstract

Asthma remains a formidable public health problem with ever increasing annual costs and prevalence. There are 300 million people with asthma worldwide. Per the Centers for Disease Control and Prevention, there are over 25 million Americans with asthma (both children and adults), i.e. one in 12 people have asthma, and this is increasing annually. Asthma results in approximately half a million hospitalizations and two million emergency department (ED) visits per year. In 2007 alone, 185 children and 3262 adults died from asthma, i.e. nine to ten patients die a day from asthma. This resulted in an annual cost of $56 billion in medical costs, lost work/school days, and early deaths. Therefore, we need novel and innovative therapies for asthma.

In this Editorial, I review results from a study by Tse et al. evaluating the therapeutic potential of statins, within the context of our current state of knowledge. I review observational studies and clinical trials, highlight some potential pitfalls in clinical trial design, and discuss important questions for future research.

Keywords

Asthma; Exacerbation; Inhaled corticosteroids; Statin; Statins

Statin use and asthma outcomes: findings, limitations, and opportunities

Tse *et al.*[1] report a large retrospective cohort observational study evaluating whether statin use in asthmatics was associated with decreased asthma-related hospitalizations and/or ED visits. A population-based administrative database was used to determine outcomes in adults on statins over a period of 12 months. Using pharmacy records, the authors defined statin use based on a measure of ‘statin exposure’. Patients were stratified into two groups according to their inhaled corticosteroid (ICS) use, a total of 3747 ICS users and 2905 non-ICS users. The authors found that among ICS users, statin use was associated with reduced

Address for correspondence: Amir A. Zeki MD MAS, Assistant Professor of Medicine, Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, UC Davis Medical Center, 4150 V Street, PSSB 3400, Sacramento, CA 95817, USA. Tel: +1 916 734 3566; Fax: +1 916 734 7924; amir.zeki@ucdmc.ucdavis.edu.

Transparency

Declaration of funding

This editorial was not funded.

Declaration of financial/other relationships

A.A.Z. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article.

odds of asthma-related ED visits (OR = 0.77, 95% CI 0.64–0.94, $p = 0.008$), but not with asthma-related hospitalizations. Non-ICS users showed no significant associations.

The strengths of this study include a large real-life cohort of asthmatics, an a priori evaluation based on ICS use, and an assessment of statin exposure up to the time of asthma-related events. This work provides indirect evidence that statins may improve important asthma outcomes such as acute exacerbations. This work along with others[2–4] provides support for a large randomized controlled trial (RCT) of a statin intervention in asthma.

As with any observational study, there are unavoidable limitations. Although the authors attempted to control for residual confounding by statin indication in their multivariate model (e.g. ischemic heart disease, stroke, diabetes), this does not fully account for the fact that the two populations are different hosts. However, even though statin users were a sicker cohort, they still did better than non-users indicating that statin use may have had a beneficial effect. Of note, lung function as a measure of baseline asthma severity, such as FEV1% predicted, was not available and therefore not accounted for in their statistical models. The authors also did not exclude patients with overlapping asthma and COPD whose response to statins may be different. Finally, a common criticism of statin observational studies is the confounding effect of the ‘healthy user effect’; however, others have attempted to account for this phenomenon and still showed a benefit to statin use[5]. To know with greater confidence, properly designed multi-center RCTs are needed.

The reason(s) for the discrepancy between asthma-related ED visits and hospitalizations in Tse *et al.*’s study is not clear. Statin use was associated with an improvement in the former but not the latter. Tse *et al.*’s findings regarding asthma-related hospitalizations differs from that of other authors[2,3]. While many reasons can be hypothesized to explain this discrepancy, one can presume that a combination of different factors led to an ED visit rather than hospitalization. Patients who were hospitalized due to their asthma may have more severe disease and, thus, it becomes important to carefully consider the hospitalized patient in future studies.

However, despite these limitations, observational studies including this one by Tse *et al.* do point us in a new direction. It provides important data to inform the planning of future asthma–statin RCTs. These data suggest that statins should be given to asthmatics already on ICS and for at least 12 months. Data already exist to support the additive or synergistic effects of statins and ICS in human asthma[6,7]. The beneficial effects of statins in reducing sputum inflammatory markers[8], yet lack of improvement in lung function, could be due to the short treatment duration (i.e. maximum 8 weeks long) of statin therapy[8,9]. The authors acknowledge that it may take years before positive effects on lung function and/or airway remodeling may be seen with statins.

Published randomized controlled trials in asthma using statins

Over the past six years or so, interest in the topic of statins as a potential therapy for airway disease such as asthma and COPD has grown. Investigators from varied countries and disciplines have evaluated the therapeutic potential of statins. However, most of these studies

have been observational in nature[2–5], and the handful of RCTs performed have yielded mixed results at best[7,10–15]. In addition, none of the clinical trials evaluated important endpoints such as acute exacerbations or ED/hospital admissions. Despite this, some benefits were noted in two of the seven reported trials. Braganza *et al.* showed a benefit in smoking asthmatics with improved quality of life (QOL) scores[11], while Cowan *et al.* reported improved ACQ (Asthma Control Questionnaire) asthma control scores, FEV1, and sputum eosinophil counts in mild asthmatics weaned off of ICS[12]. While statins cannot yet be recommended for the treatment of asthma in the absence of stronger results from RCTs, significant opportunities remain as this area is ripe for investigations on several levels.

It is well accepted that the statins have revolutionized the treatment of cardiovascular diseases. In addition to reducing cardiovascular events and deaths due to myocardial infarctions[16], statins amazingly reverse atherosclerotic vascular wall remodeling[17] thereby improving coronary blood flow. This key observation is not seen over a scale of weeks or months, but rather over years of treatment. Therefore, the temporal relationship between statin use and the asthma outcome of interest becomes a very important point of consideration. Might the same thing be possible in asthmatic airways with respect to adverse structural remodeling and luminal narrowing? This is perhaps the single most important point to be raised regarding the lack of efficacy in the aforementioned asthma–statin RCTs – the treatment duration. The above RCTs studied a statin intervention over 4 or 8 weeks. Based on Tse *et al.*'s findings and that of others, we may need 1 to 2 years of statin treatment before acute exacerbations and/or oral corticosteroid use are reduced; and perhaps longer duration for anti-remodeling effects.

Potential benefits in asthma

Given the biological plausibility of the statins with respect to lung and airway diseases in particular, and given their pleiotropic immunomodulatory effects[18,19], it is reasonable to think that the statins could have a beneficial effect in asthma (Figure 1). This would require the correct experimental conditions, the right type of statin, and the appropriate patient population that is most likely to benefit.

Many additional areas of investigation are needed in order to better understand statins' potential benefits and/or potential harms. To date, we still do not know whether an orally ingested statin even reaches the airway compartment, let alone the bronchial epithelium – but we assume it does. The answer to this important question has clear implications for direct statin effects on airway resident cells such as epithelial, mesenchymal (e.g. fibroblasts, airway smooth muscle), and endothelial cells, including the resident immune cells (e.g. macrophages and airway dendritic cells).

The immune and endothelial effects of statins are generally well established in the cardiovascular literature. Some work has already been done in epithelial and mesenchymal cells, but we are in the early stages. For instance, simvastatin inhibits airway smooth muscle cell proliferation in vitro[20] and airway hyperreactivity in vivo[21,22], while inducing apoptosis in airway mesenchymal cells[23,24]. Might statins mitigate airway smooth muscle cell mass and thereby reduce airflow obstruction? Statins also have differential effects on epithelial

cytokine production, with most publications indicating inhibition of pro-inflammatory cytokines[25–28]. Furthermore, detailed mechanistic studies are also needed in order to elucidate the underlying mechanisms involved. Thus, the central question of direct statin effects on airway structural cells in the human host, and the logical link to route of administration and drug development, remain critical areas for research.

Questions for future clinical studies

As one contemplates the next steps in research, the following questions arise:

- What is the ideal route of administration, i.e. oral versus inhaled versus both?
- What are statins' effects on airway epithelial mucosal immunity and barrier integrity?
- Which combination treatments (ICS, LABA, LAMA, LTRA, etc. ± statin) might have the best effect on reducing asthma exacerbations and airway remodeling/ disease progression, while improving lung function?
- Which class of statin has the greatest potential for benefiting asthmatics (i.e. hydrophilic versus hydrophobic statins)?
- What about the pediatric asthma population? When is it too early (or too late) to begin treatment? Is it safe to use a statin in this population?
- What lung-specific versus systemic biomarkers (or gene signatures) might predict a 'statin-responsive' asthmatic subgroup?
- What asthma phenotype or sub-phenotype is most likely to benefit?

Many more questions exist and will likely arise. While tempered optimism is appropriate regarding statins in asthma, given the widespread use of statins worldwide, serious efforts should be undertaken to answer the above questions. Beyond their fascinating biological activities, the statins have the potential to be an important adjunctive therapy in our treatment armamentarium. Advances in this area might usher in the next innovative yet hopefully inexpensive therapy for asthma.

References

1. Tse SM, Charland SL, Stanek E, et al. Statin use in asthmatics on inhaled corticosteroids is associated with decreased risk of emergency department visits. Curr Med Res Opin. 2014; 30:685–93. [PubMed: 24219830]
2. Huang CC, Chan WL, Chen YC, et al. Statin use in patients with asthma: a nationwide population-based study. Eur J Clin Investig. 2011; 41:507–12. [PubMed: 21128938]
3. Lokhandwala T, West-Strum D, Banahan BF, et al. Do statins improve outcomes in patients with asthma on inhaled corticosteroid therapy? A retrospective cohort analysis. BMJ. 2012; 2:1–8.
4. Zeki AA, Oldham J, Wilson M, et al. Statin use and asthma control in patients with severe asthma. BMJ Open. 2013; 3:1–10.
5. Alexeeff SE, Litonjua AA, Sparrow D, et al. Statin use reduces decline in lung function: VA Normative Aging Study. Am J Respir Crit Care Med. 2007; 176:742–7. [PubMed: 17673694]
6. Maneechotesuwan K, Kasetsinsombat K, Wamanuttajinda V, et al. Statins enhance the effects of corticosteroids on the balance between regulatory T cells and Th17 cells. Clin Exp Allergy. 2013; 43:212–22. [PubMed: 23331562]

7. Maneechotesuwan K, Ekjiratrakul W, Kasetsinsombat K, et al. Statins enhance the anti-inflammatory effects of inhaled corticosteroids in asthmatic patients through increased induction of indoleamine 2, 3-dioxygenase. J Allergy Clin Immunol. 2010; 126:754–62.e1. [PubMed: 20920765]
8. Yuan C, Zhou L, Cheng J, et al. Statins as potential therapeutic drug for asthma? Respir Res. 2012; 13:108. [PubMed: 23176705]
9. Si X, Zhang S, Huo L, et al. Statin therapy does not improve lung function in asthma: a meta-analysis of randomized controlled trials. J Int Med Res. 2013; 41:276–83. [PubMed: 23569033]
10. Hothersall EJ, Chaudhuri R, McSharry C, et al. Effects of atorvastatin added to inhaled corticosteroids on lung function and sputum cell counts in atopic asthma. Thorax. 2008; 63:1070–5. [PubMed: 18757458]
11. Braganza G, Chaudhuri R, McSharry C, et al. Effects of short-term treatment with atorvastatin in smokers with asthma – a randomized controlled trial. BMC Pulmonary Medicine. 2011; 11:16. [PubMed: 21473764]
12. Cowan DC, Cowan JO, Palmay R, et al. Simvastatin in the treatment of asthma: lack of steroid-sparing effect. Thorax. 2010; 65:891–6. [PubMed: 20861293]
13. Menzies D, Nair A, Meldrum KT, et al. Simvastatin does not exhibit therapeutic anti-inflammatory effects in asthma. J Allergy Clin Immunol. 2007; 119:328–35. [PubMed: 17141851]
14. Fahimi F, Salamzadeh J, Jamaati H, et al. Do statins improve lung function in asthmatic patients? A randomized and double-blind trial. Iranian J Pharmaceut Sci. 2009; 5:13–20.
15. Moini A, Azimi G, Farivar A. Evaluation of atorvastatin for the treatment of patients with asthma: a double-blind randomized clinical trial. Allergy Asthma Immunol Res. 2012; 4:290–4. [PubMed: 22950035]
16. Mills EJ, Rachlis B, Wu P, et al. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008; 52:1769–81. [PubMed: 19022156]
17. Nicholls SJ, Grasso AW, Schoenhagen P, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA. 2007; 297:499–508. [PubMed: 17284700]
18. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nat Rev Immunol. 2006; 6:358–70. [PubMed: 16639429]
19. Liao J, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005; 45:89–118. [PubMed: 15822172]
20. Takeda N, Kondo M, Ito S, et al. Role of RhoA inactivation in reduced cell proliferation of human airway smooth muscle by simvastatin. Am J Respir Cell Mol Biol. 2006; 35:722–9. [PubMed: 16858009]
21. Zeki AA, Franzi L, Last J, Kenyon NJ. Simvastatin inhibits airway hyperreactivity: implications for the mevalonate pathway and beyond. Am J Respir Crit Care Med. 2009; 180:731–40. [PubMed: 19608720]
22. Ahmad T, Mabalirajan U, Sharma A, et al. Simvastatin improves epithelial dysfunction and airway hyperresponsiveness: from asymmetric dimethylarginine to asthma. Am J Respir Cell Mol Biol. 2011; 44:531–9. [PubMed: 20558777]
23. Ghavami S, Mutawe MM, Sharma P, et al. Mevalonate cascade regulation of airway mesenchymal cell autophagy and apoptosis: a dual role for p53. PloS One. 2011; 6:e16523. [PubMed: 21304979]
24. Ghavami S, Mutawe MM, Hauff K, et al. Statin-triggered cell death in primary human lung mesenchymal cells involves p53-PUMA and release of Smac and Omi but not cytochrome c. Biochim Biophys Acta. 2010; 1803:452–67. [PubMed: 20045437]
25. Iwata A, Shirai R, Ishii H, et al. Inhibitory effect of statins on inflammatory cytokine production from human bronchial epithelial cells. Clin Exp Immunol. 2012; 168:234–40. [PubMed: 22471285]
26. Sakoda K, Yamamoto M, Negishi Y, et al. Simvastatin decreases IL-6 and IL-8 production in epithelial cells. J Dent Res. 2006; 85:520–3. [PubMed: 16723648]
27. Murphy DM, Forrest IA, Corris PA, et al. Simvastatin attenuates release of neutrophilic and remodeling factors from primary bronchial epithelial cells derived from stable lung transplant recipients. Am J Physiol Lung Cell Mol Physiol. 2008; 294:592–9.

28. Zeki AA, Thai P, Kenyon NJ, Wu R. Differential effects of simvastatin on IL-13-induced cytokine gene expression in primary mouse tracheal epithelial cells. Respir Res. 2012; 13:38. [PubMed: 22583375]

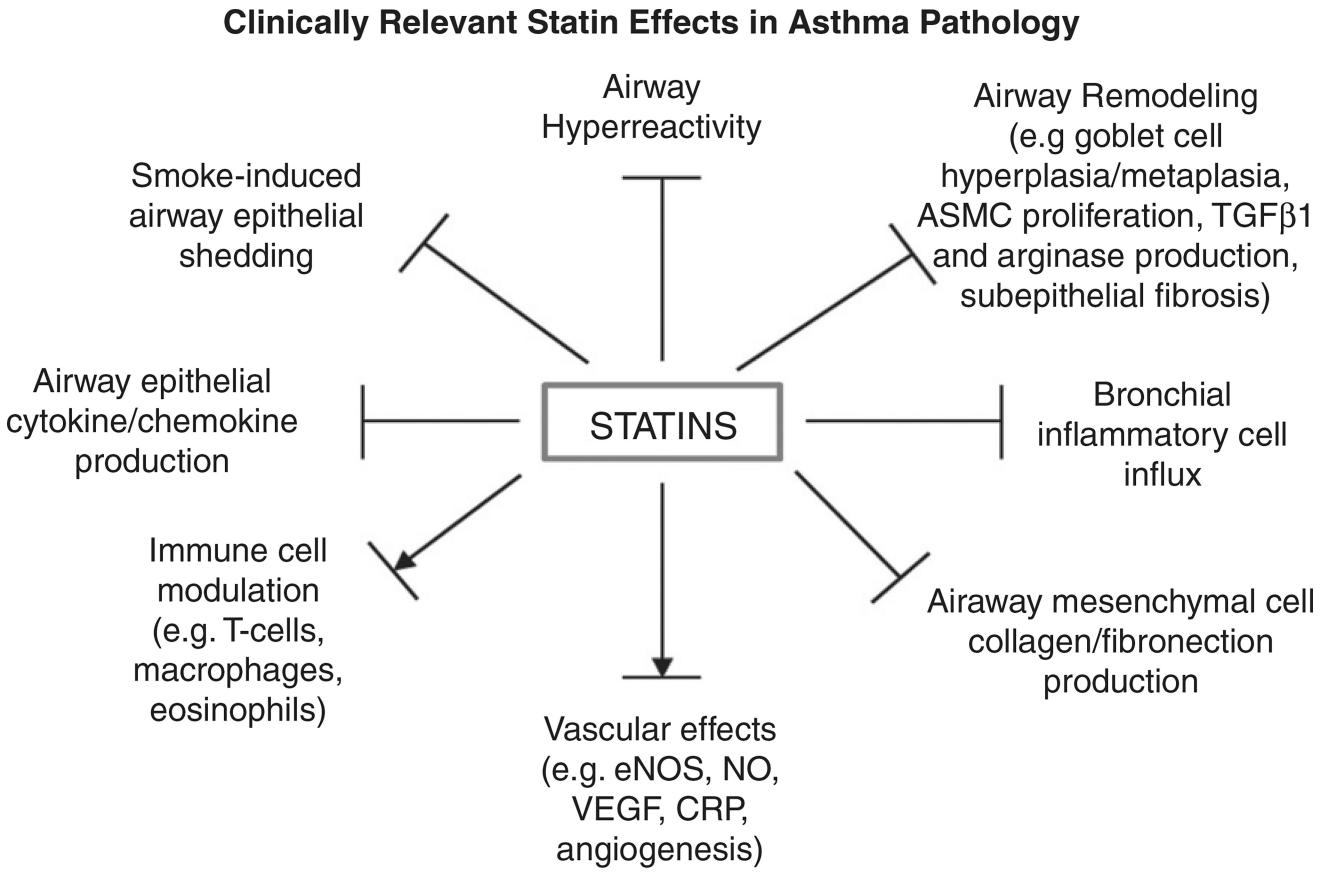

Figure 1.

Clinically relevant statin effects in asthma pathology.

Abbreviations: ASMC = airway smooth muscle cell, TGFβ1 = transforming growth factor-β1, eNOS=endothelial nitric oxide synthase, NO = nitric oxide, VEGF = vascular endothelial growth factor, CRP = C-reactive protein. *Lines alone represent statin inhibition, lines with arrow heads represent statin modulation*.