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Statin Therapy for Asthma: Is Scientific Evidence in Favour or Against?

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ABSTRACT

Asthma is known to be an inflammatory condition. The 3-HMG-CoA reductase inhibitors (statins) used to lower serum cholesterol level, have been found to exhibit anti-inflammatory properties.

Consequently, it has been suggested that statins may affect the course and possibly reduce the severity of asthma. However, there are conflicting reports over the beneficial effects of statins in asthma. Hence, there is need for caution and high index of suspicion amongst care givers, that though available evidence points to their potential usefulness, statins may also precipitate and aggravate asthmatic conditions.

Key words: Asthma, cholesterol, Immunomodulation, Inflammation, Scientific evidence and statins.

INTRODUCTION

The 3-hydroxy-3-methyl glutaryl Coenzyme A (HMG–CoA) reductase inhibitors otherwise known as statins are one of the most prescribed medications in clinical use today. They are effective in lowering serum cholesterol level by inhibiting 3-HMG–CoA reductase that mediates the rate–limiting step in sterol biosynthesis.

Statins have been found effective in treating hyperlipidemia and in preventing morbidity and mortality associated with coronary heart disease most especially in high risk population[1]. Certain findings have demonstrated the therapeutic potential of statin–sensitive pathways in allergic asthma. However, other reports have shown that the condition of asthma patients further deterriorate after statin treatment.

This paper attempts to examine the risk-benefit profile of statin use in asthma patients, moreso, considering the widespread use of statins in the general population, a significant number of whom may have asthma.

Anti–inflammatory profile of statins in asthma

Asthma is associated with inflammation, hyper-reactive swollen airways and constriction of the bronchial muscles. Inflammation plays a crucial role in the pathophysiology of asthma. Mast cells have since been implicated in early asthmatic reaction.

The T-helper 2 (Th2) cells trigger a cascade of events that culminate in the excessive production of a class of antibody called immunoglobulin E (IgE) which binds to mast cells. The mast cells release histamine, cytokines and other immune system mediators promoting vascular changes, mucus production and recruitment of more inflammatory cells.

Evidence has shown that the clinical benefit of statins could be attributed to a reduction in anti-inflammatory response rather than an

improvement in endothelial function[2]. Statins regulate inflammatory cell adhesion and endothelial function. Statins inhibit the expression of ICAM–1 (intracellular adhesion molecules) on human monocytes and prevent lipopolysaccharide (LPS) induced ICAM–1 expression in endothelial cells via inhibition of rho activity[3,4].

Statins are known to exhibit impressive immunomodulatory effects[5]. They suppress T-helper1 (Th1) cell development and promote T-helper 2 (Th 2) cell polarization from CD_4 cells *in vitro*[6]. Statins also act as direct inhibitors of class II major histocompatibility antigen (MHC II) expression and interferon gamma thereby inhibiting T cell activation[7]. The various effects of statins on lymphoid cell function have been demonstrated. They include suppression of natural killer cell proliferation activity by simvastatin *in vitro*[8-10]. Statins exert immunomodulatory effects by binding to leukocyte function antigen 1 (LFA1) as this integrin did not only play a role in leucocyte adhesion but did also work as T-cell co-stimulator[11]. It is, therefore, reasonable to suggest that statins have beneficial anti-inflammatory action. However, findings from various studies suggest otherwise.

Evidence in favour or against statin use in asthma patients

A study reported at the annual meeting of the American College of Allergy, Asthma and Immunology in Boston revealed negative effects attributable to statins leaving pulmonologists astonished due to previous reports demonstrating beneficial effects in asthma. In the said study, after one year, patients on statins were 35% worse on a lung function test relative to commencement of study. This was as compared to a decrease in lung function reported in patients not taking statins which was 14% worse in comparison to commencement of study.

Another study retrospectively reviewed 759 medical records of consecutive patients with asthma to identify patients with extrinsic asthma who had at least 4 physician visits over 1 year. The study compared patients who never received statins with those that were treated with statins after initial asthma evaluation. Results showed a statistically significant 3% to 5% median worsening of forced expiratory volume in one second (FEV1) at all time points for the statin group compared with the non-statin group[12].

Analysis of a claims database reported by the American Academy of Allergy, Asthma and Immunology showed that asthma patients who took statins were 33% less likely to have an asthma related hospitalization or emergency room visit during the next year.

The Medco Health Solutions analysis on 6,600 patients identified poorly controlled asthmatic on the basis of having received prescription for inhaled corticosteriods and at least one hospitalization or emergency room (ER) visits during the preceding year[13]. Data indicated that hospitalization or emergency room visits the following year were respectively 18% and 44% lower; the effect being nearly identical for hospitalization and ER visits with odd ratios of 0.73 and 0.72 respectively ($P<0.001$) for both. Interestingly, a different analysis by researchers from Kaiser Permanente in San Diego found no evidence in support of statin use for severe asthma[14]. It was shown in the said study that emergency room visits and hospitalizations were significantly more common in the statin-treated patients at baseline compared to non-statin group. It can be deduced from outcome of the study that asthma patients selected for statin treatment appear to have inherently more severe disease which statin treatment is unable to suppress. It should be noted that the Medco study did not control as many variables as the Kaiser study, hence, it may be possible that statins can help at least a certain population of asthma patients especially those with less severe initial disease.

The report of a randomised placebo controlled trial of simvastatin in asthma patients who had all anti-inflammatory medication withdrawn showed there was no improvement in asthma symptoms, pulmonary function and measures of asthmatic inflammation including exhaled nitric oxide, sputum/serum eosinophils, serum C–reactive protein and salivary eosinophilic cationic protein[15]. The result of another randomised clinical trial involving atorvastatin added to inhaled corticosteriods as compared with subjects treated

with inhalational corticosteroid alone concluded that statins were ineffective for short term therapy of allergic asthma[16].

Experimental evidence supporting statin use showed high dose simvastatin (40mg/kg) attenuated eosinophil driven inflammation in a murine model of ovalbumin induced asthma. This was mediated by suppressing T-lymphocyte secretion of interlukins IL4 and IL5[17]. A similar study revealed that fluvastatin decreased peripheral blood mononuclear cell proliferation production of IL5 and interferon gamma; however, in contrast with earlier studies, fluvastatin did not decrease MHCII expression on dendritic cells or lymphocytes[18]. A large matched cohort study reported that use of statins was associated with a significantly decreased risk of chronic obstructive pulmonary disease (COPD) and other respiratory diseases[19]. A study reported that statin use attenuated the normal pulmonary function measurements performed prospectively in 803 elderly men in the Normative Aging Study[20].

A study suggested that pravastatin may be useful therapy for the treatment of asthma[21]. This was based on the finding that pravastatin inhibits antigen sensitisation presentation in the lungs of ovalbumin sensitized mice and also attenuated albumin induced cell proliferation, IL5 production and eosinophilic airway inflammation. However, a number of caveats make this interpretation a bit controversial. The researchers acknowledged that experimental ovalbumin induced asthma is very different from human asthma, making it difficult to predict the effects of therapeutic interventions in humans. It was also acknowledged that the mice were given a large dose of pravastatin (10mg/kg/day) since normal dose of 2mg/kg/day did not attenuate allergic airway inflammation. Hence, the administered dose was more than 30 times the dose used in humans routinely for treatment of hyperlipidemia. Again, being a short term study, it is not obvious that long term use of statins would continue to demonstrate immunomodulation or non-linear effect on the immune system.

CONCLUSION

The implication of this review underlies the need for more caution amongst physicians and allergy specialists caring for asthma patients.
There is need for high index of suspicion amongst care givers, that though there is available evidence pointing to the potential usefulness of statins in helping patients with asthma; it should also be noted that statins by decreasing the levels of Th1 cells will tilt the balance in favour of production of Th2 cells known to precipitate and aggravate asthma.

However, with the glaring prospects of the complete sequencing of the human genome, coupled with the availability and affordability of whole genome sequencing technologies; further research is invaluable in identifying genetic variants that will distinguish individual asthma patients who may or may not benefit from statin therapy.

REFERENCES

1. Bhatnagar D., Soran H. and Durrington P. N. Hypercholesterolemia and its management. *BMJ.* **337**: 993 (2008).
2. Dangas G., Badimon J.J., Smith D.A. *et al.* Pravastatin therapy in hyperlipidemia: effects on thrombus formation and the systemic hemostatic profile. *J. Am. Coll. Cardiol.* **33**: 1294-1304 (1999).
3. Niwa S., Totsuka T. and Hoyashi S. Inhibitory effects of fluvastatin, an HMG–CoA reductase inhibitor on the expression of adhesion molecules on human monocyte cell line. *Int. J. Immunopharmacol.* **18**: 669-675 (1996).
4. Takeuchi S., Kawashima S., Rikitake Y., Ueyama T., Inoue N., Hirata K. and Yokoyama M. Cerivastatin suppresses lipopolysaccharide induced ICAM–1 expression through inhibition of Rho GTPase in BAEC. *Biochem. Biophys. Res. Commun.* **269**: 97-102 (2001).
5. Greenwood J., Steinman L. and Zamvil S.S. Statin therapy and antoimmune disease: from protein prenylation to

immunomodulation. *Nat. Rev. Immunol*. **6**: 358-370 (2006).

6. Hakamada-Taguchi R., Uehara Y., Kuribayashi K. *et al*. Inhibition of hydroxymethyl glutaryl-coenzyme A reductase reduces Th1 development and promotes Th2 development. *Circ. Res.* **93**: 948-956 (2003).
7. Kwak B., Mulhaupt F., Myit S. and Mach F. Statins as newly recognised type of immunomodulator. *Nat Med*. 6:139 –1402 (2000)
8. Cuthbert J.A. and Lipsky P.E. Sterol metabolism and lymphocyte responsiveness: inhibition of endogenous sterol synthesis prevents mitogen induced human T-cell proliferation. *J. Immunol.* **126**: 2093-2099 (1981).
9. Cutts J. L. and Bankhurst A.D. Suppression of lymphoid cell function *in vitro* by inhibition of 3-hydroxy-3-methyl glutaryl co-enzyme A reductase by lovastatin. *Int. J. Immunopharmacol.* **11**: 863-869 (1989).
10. Kurakata S., Kada M., Shimada Y., Komai T. and Nomoto K. Effects of different inhibitors of 3-hydroxy-3-methyl glutaryl co-enzyme A reductase: pravastatin and simvastatin on sterol synthesis and immunological functions in human lympocytes *in vitro*. *Int. J. Immunopharmacol.* **34**: 51-61 (1996).
11. Weitz Schmidt G., Welzenbach K., Brinkmann V., Kamata T., Kallen J., Bruns C., Cotton S., Takada Y. and Hommel U. Statins selectively inhibit leukocyte function antigen 1 by binding to a novel integrin site. *Nat. Med.* **7**: 687-692 (2001).
12. Ostroukhova M., Kouides R.W. and Friedman E. The effect of statin therapy on allergic patients with asthma. *Ann. Allergy Asthma Immunol.* **103**(6): 463-468 (2009).
13. Stanek E., Aubert R., Xia F. *et al.* Statin exposure reduces the risk of asthma-related hospitalizations and emergency room visits in asthmatic patients on inhaled corticosteroids. *J. Allergy Clin. Immunol.* 123:S65.
14. Christiansen S. *et al.* HMG-CoA reductase inhibitors and asthma severity. *J. Allergy Clin. Immunol.* **123**: S84.
15. Menzies D., Nair A, Meldrum K.T. *et al.* Simvastatin does not exhibit therapeutic anti-inflammatory effects in asthma. *J. Allergy Clin. Immunol.* **119**: 328–335 (2007).
16. Hothersall E.J, Chandhuri R., McSharry C. *et al.* Effects of atorvastatin added to inhaled corticosteroids on lung function and spùtum cell counts in atopic asthma. *Thorax*. **63**: 1070-1075 (2008).
17. Mckay A., Leung B.P., Mclnnes I.B *et al*. A novel anti-inflammatory role of simvastatin in a murine model of allergic asthma. *J. Immunol.* **172**: 2903-2908 (2008).
18. Samson K.T., Minoguchi K., Tanaka A. *et al.* Inhibitory effects of fluvastatin on cytokine and chemokine production by peripheral blood mononuclear cells in patients with allergic asthma. *Clin. Exp. Allergy*. **36**: 475-482 (2006).
19. van Gestel Y.R., Hoeks S.E., Sin D.D. *et al.* Effect of statin therapy on mortality in patients with peripheral arterial disease and comparison of those with versus without associated chronic obstructive pulmonary disease. **102**: 192-196 (2008).
20. Alexeeff S.E., Litonjua A.A., Sparrow D. *et al.* Statin use reduces decline in lung function: VA Normative Aging Study. *Am. J. Respir. Crit. Care Med*. **176**: 742-747 (2007).
21. Imamura M., Okunishi K., Ohtsu H. *et al.* Pravastatin attenuates allergic airway inflammation by suppressing antigen sensitization, interleukin 17 production and antigen presentation in the lung. *Thorax*. **64**: 44-49 (2009).