Name of Sponsor/Company
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Title of Study
A Proof of Concept Study to Investigate the Use of Simvastatin as a Putative Anti-Inflammatory Agent in Asthma

Investigators
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Study centre(s)
Asthma & Allergy Research Group

Publication (reference)
MENZIES D, NAIR A, MELDRUM K, FLEMING D, BARNES M, LIPWORTH BJ. Simvastatin does not exhibit therapeutic anti-inflammatory effects in asthma. J Allergy Clin Immunol 2007;119:328-335

Date of first enrolment	**Phase of development**
June 2005	Phase IV
Date of last completed	
May 2006	

Objectives
To evaluate the in vivo therapeutic potential of simvastatin as an anti-inflammatory agent in patients with asthma.

Methodology
Potential signal from treatment effect was optimized by withdrawing all anti-inflammatory treatment for the duration of the study. Participants received 1 month of daily simvastatin and 1 month of daily placebo in a randomized, double-blind crossover trial. A total of 16 patients completed per protocol. Asthmatic inflammation was evaluated by measuring exhaled tidal nitric oxide, alveolar nitric oxide, sputum and peripheral eosinophil count, methacholine hyper-responsiveness, salivary eosinophilic cationic protein, and C reactive protein. Measurements of dynamic and static lung volumes and of cholesterol were also made.

Number of patients planned
20 patients recruited for 16 to complete per protocol

Number of patients analysed
16

Diagnosis and main criteria for inclusion
Mild-to-moderate asthma, documented normal liver function, $FEV_1 \geq 60\%$ predicted, on a regular Maintenance ICS dose of $\leq$ 2000 mg daily of beclomethasone or equivalent were invited to participate. Patients were excluded if pregnant, smokers, already receiving or known to be allergic to statins, or had an exacerbation of their asthma requiring treatment with oral corticosteroids during the preceding 3 months.

Test product dose

Arm A
Simvastatin 20 mg (2 weeks)
Simvastatin 40 mg (2 weeks)

Arm B
Placebo tablet (4 weeks)

Duration of treatment
8 weeks (2 treatment periods of 4 weeks)

Reference therapy
Placebo Simvastatin (see Test Product Dose)

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Primary Endpoint
FE_{NO}

Secondary Endpoints
All other surrogate markers of bronchial inflammation and MCh responsiveness

Statistical methods
SPSS version 12 (SPSS Inc, Chicago, Ill) was used to perform the statistical analysis. The study was designed with 90% power to detect a 25% reduction in FE_{NO} with 12 patients completed per protocol; all other endpoints were considered secondary. Data were initially assessed for normality using distribution plots; any non-normally distributed data were log-transformed before analysis. Data were evaluated by an overall ANOVA with treatment, subject, and sequence as cofactors, followed by Bonferroni-corrected pairwise comparisons with a 2-tailed α-error set at 0.05.

Summary Conclusions

Results
After initial withdrawal of usual asthma medication, there was a 1.43 geometric mean fold increase (ie, 43% difference) in fraction of exhaled nitric oxide (95% CI, 1.15 to 1.78; P = .004). Compared with placebo, simvastatin led to a 0.86 geometric mean fold decrease (95% CI, 0.7 to 1.04; P = .15) in exhaled nitric oxide (ie, a 14% difference), and a –0.18 doubling dilution shift (95% CI, –1.90 to 1.55; P = 1.0) in methacholine hyper-responsiveness. There were no significant differences in other inflammatory outcomes, lung volumes, or airway resistance between simvastatin and placebo. Treatment with simvastatin led to a significant reduction (P < .005) of total and low-density lipoprotein cholesterol.

Conclusion
There is no evidence to suggest simvastatin has anti-inflammatory activity in patients with asthma.

Date of the report: 25.05.2016