Simvastatin in the treatment of asthma: lack of steroid-sparing effect

Douglas C Cowan, Jan O Cowan, Rochelle Palmay, Avis Williamson, D Robin Taylor

ABSTRACT

Background Statins have anti-inflammatory actions which in theory are potentially beneficial in asthma. Small trials have failed to show a significant benefit, but a systematic study to evaluate the steroid-sparing effect of statin treatment has not been carried out.

Methods A randomised, placebo-controlled, crossover trial was conducted of simvastatin 40 mg at night with simultaneous stepwise reduction of fluticasone propionate dose until loss of control occurred, followed by an increase until regain of control (‘minimum’ dose required) in 51 patients with asthma and sputum eosinophils (steroid-free) ≥2%.

Results 43 patients completed the study. There was no significant difference in ‘minimum’ inhaled corticosteroid (ICS) dose required between simvastatin and placebo: (median (IQR) 50 μg daily (0–250) vs 100 μg daily (0–250), p = 0.931). ‘Minimum’ dose distribution was similar (p = 0.269). The fluticasone dose at which loss of control occurred did not differ significantly between simvastatin and placebo (p = 0.404). In patients with loss of control in both treatment arms, fluticasone dose at loss of control was similar with simvastatin and placebo (median (IQR) 50 μg daily (0–100) for both, p = 0.620). In those patients who reached 0 μg day (n = 18), Asthma Control Questionnaire (ACQ) was lower (p = 0.037), forced expiratory volume in 1 s (FEV1) higher (p < 0.01) and sputum eosinophils lower with simvastatin compared with placebo (9.5% compared with 25.4%, p = 0.033).

Conclusions Simvastatin does not have clinically important steroid-sparing effects in patients with eosinophilic asthma. In the absence of steroid, simvastatin is associated with minor improvements in symptoms and lung function, and a reduction in sputum eosinophils.

Clinical trial number ACTRN12606000531516.

INTRODUCTION

Statins have anti-inflammatory as well as cholesterol-lowering effects.1 They may be beneficial in cardiovascular disease,2 multiple sclerosis3 and rheumatoid arthritis.4 In chronic obstructive pulmonary disease (COPD),5 their use is associated with reduced decline in lung function,6 improved survival following exacerbations7 and increased exercise capacity.8

In asthma, there are theoretical reasons why statins might exert therapeutic effects. Their actions include reducing both T cell proliferation and activation, and leucocyte migration.9 In animal models, statins inhibit eosinophilic infiltration into the lung,10,11 reduce airway hyper-responsiveness (AHR),12 and reverse impaired β-adrenoceptor responsiveness induced by airway inflammation.13

In human tissue, statins reduce mast cell degranulation,14 enhance inflammatory cell apoptosis15 and inhibit airway smooth muscle proliferation.16

To our knowledge, only two clinical studies investigating statins in asthma have been published.17,18 The scope of these was limited. The first was of short duration (1 month), with a small number of patients (n = 16).17 In the second, inhaled corticosteroid (ICS) treatment was continued, and anti-inflammatory and steroid-sparing effects may have been masked.18

Our aim was to assess the steroid-sparing effects of simvastatin in patients with asthma. Our hypothesis was that with simvastatin, patients would require lower doses of ICS to maintain control. We conducted a randomised, double-blind, placebo-controlled, crossover study of simvastatin in which down-titration of ICS treatment was systematically undertaken.

METHODS

See also the Online repository.

Patients

Patients with stable persistent asthma were enrolled. Exclusion criteria are given in the Online repository.

Phase 1

All patients completed a 2-week run-in on regular medications, then ICS treatment was withdrawn until loss of control (LOC) or 28 days. This was followed by an open-label trial of inhaled fluticasone (1000 μg daily for ≥28 days). The aim of Phase 1 was to define the off-steroid inflammatory cell phenotype and the magnitude of steroid responsiveness. For further details, see Cowan et al.19

Phase 2

Patients proceeded to randomisation if, off steroid, they demonstrated one of the following: a provocation dose of hypertonic saline causing a 15% fall in forced expiratory volume in 1 s (FEV1) (PD15) of <12 ml20; a provocation dose of methacholine causing a 20% fall in FEV1 (PD20) of <8 μmol21; or an increase in FEV1 postbronchodilator ≥12%.22 All randomised patients had sputum eosinophilia ≥2%:23 non-eosinophilic patients were excluded.

Study design

This was a randomised, double-blind, placebo-controlled, crossover trial of simvastatin, with stepwise down-titration of ICS dose during each treatment arm. Patients took a capsule containing either active drug (simvastatin 40 mg; Lipex, Merck Sharp Dohme, Auckland, New Zealand) or matching
placebo once daily at night. The investigators were blinded to
treatment allocation. In addition, each month, patients were
supplied with two inhalers (A and B) and took one puff of inhaler
A in the morning and one puff of inhaler B in the evening. The ICS
dose was blinded to the patient by coupling unlabelled inhaler
sleeves with actuators containing fluticasone 50, 125 or 250 µg, or
placebo (0 µg) (Flixotide, GlaxoSmithKline, Greenford, UK).
Different A and B combinations provided for daily doses of 0, 50,
100, 250 or 500 µg.

Patients were commenced at a dose of fluticasone of 500 µg/
day. If asthma was not controlled during the first month, the
dose was stepped up to 1000 µg/day for 1 month before
commencing down-titration. If asthma was controlled, patients
were given the next treatment pack and returned a month later.
The dose of fluticasone was then stepped down at monthly
intervals until LOC based on a priori criteria24 (figure 1). At
LOC, or after 1 month taking 0 µg/day fluticasone, sputum
induction and AMP challenge were performed. Patients with no
LOC at 0 µg/day were crossed over to the alternative treatment
and the sequence was repeated. Patients who experienced LOC
then received fluticasone at a dose one step up from the one at
which LOC had occurred. They were reviewed monthly with
stepwise increases in fluticasone until control was regained
(deemed to be the ‘minimum dose requirement’). Sputum
induction and AMP challenge were repeated at the ‘minimum’
dose, and patients then proceeded to the alternative arm.

Daytime symptoms, night waking, bronchodilator use and peak
flows were recorded daily.

Procedures at monthly reviews
Patients completed the Asthma Control Questionnaire (ACQ),
Asthma Control Test (ACT) and Asthma Quality of Life
Questionnaire (AQLQ) before having their fraction of exhaled
nitric oxide (FeNO) and spirometry measured.

Ethical and safety considerations
All patients gave written informed consent. Safety procedures,
including adverse drug event monitoring, are documented in the
Online repository. Ethical approval was obtained from the
Lower South Regional Ethics Committee, New Zealand.

This study was registered with the Australian New Zealand
Clinical Trials Registry (ACTRN12606000531516).

Study size and statistical analyses (see Online repository)
The primary end point was ‘minimum’ ICS dose requirement.
Secondary end points were ICS dose at LOC, and number of
patients without LOC after ICS withdrawal. Based on previous
data,25 and using a SD of 200 µg for mean daily fluticasone dose
requirement, it was calculated that to demonstrate the superi-
ority of simvastatin in reducing the ‘minimum’ dose require-
ment by 100 µg, 35 patients would be required (power=80%,
α=0.05 and β=0.2). Additional patients were recruited to allow

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**Figure 1** Protocol for the first arm of study (second arm identical). Patients were randomised to either simvastatin 40 mg at night or placebo during the first arm, and were crossed over to receive the alternative treatment in the second arm. Monthly changes in daily fluticasone dose are shown in boxes. Subjects commenced on 500 µg daily, and stepwise reduction occurred each month until either loss of control (LOC) or 0 µg/day was reached. Sputum induction and AMP challenge were then performed. Subjects reaching 0 µg/day without LOC (‘minimum required’ dose = 0 µg/day) then proceeded to the second arm. Subjects with LOC were provided with the fluticasone dose one step up from that at which LOC occurred. They were reviewed monthly with stepwise increase in fluticasone dose each month until regain of control (ROC) occurred (‘minimum required’ dose), at which time sputum induction and AMP challenge were repeated before progressing to the second arm. *Criteria for loss of control were based on diary data and spirometry from the last 2 weeks of the Phase 1 trial of fluticasone. ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid (fluticasone).*
for a drop-out rate of 25%. Paired survival analysis was used to compare the proportions of patients who reached LOC at each treatment step on simvastatin and placebo, using Cox proportional hazards regression clustered on the individual. Proportions with LOC on simvastatin and placebo were compared using McNemar test. ICS dose at LOC and ‘minimum’ ICS dose on simvastatin and placebo were compared using Wilcoxon signed rank sum tests. Other comparisons were made using paired t tests and Wilcoxon signed rank sum tests. For purposes of the study, asthma control was deemed to be the absence of criteria used to define LOC. Statistical correction for multiple comparisons was not undertaken and the possibility exists that some results occurred by chance despite a p value <0.05.

**RESULTS**

Fifty-one subjects were randomised; 43 completed both treatment arms. Baseline characteristics are shown in table 1. There were eight withdrawals: three before commencing treatment (pregnancy, deranged liver function, withdrawal of consent); four during the simvastatin arm (muscle pain, rash, troublesome asthma, relocation); and one during the placebo arm (pregnancy). Data for these eight subjects were not analysed; some asthma, relocation); and one during the placebo arm (pregnancy, deranged liver function, withdrawal of consent); four during the simvastatin arm (muscle pain, rash, trouble-

LOC during stepwise ICS dose reduction

With down-titration, the number of subjects who lost control at LOC during stepwise ICS dose reduction did not differ significantly between simvastatin and placebo (p=0.404; figure 2). LOC occurred in 26 subjects (60%) during both simvastatin and placebo arms, in 5 (7%) during the simvastatin arm only, and in 6 (14%) during the placebo arm only. There was no order effect. In 8 (19%), LOC did not occur in either arm (p=0.508), and thus for this subgroup, ‘minimum’ ICS dose was 0 μg/day with both simvastatin and placebo. In patients with LOC during both treatment arms (n=26), the fluticasone dose at LOC was not significantly different between the simvastatin and placebo arms; median (IQR) for both, 50 μg/day (0–100) (p=0.620).

‘Minimum’ fluticasone dose and asthma control

At ‘minimum’ fluticasone dose, ACQ was similar with both simvastatin and placebo (median (IQR) 0.3 (0.0–1.1) and 0.7 (0.3–1.2), respectively, p=0.171) (table 2). There was no significant difference in the ‘minimum’ fluticasone dose between the simvastatin and placebo arms; median (IQR) 50 μg/day (0–250) and 100 μg/day (0–250), respectively (p=0.931). The distribution of ‘minimum’ doses with simvastatin or placebo did not differ significantly (χ² = 9.94, p=0.269; figure 3). Similarly, ACT, AQoL, FEV₁ and AHR were not significantly different between treatment arms at ‘minimum’ fluticasone dose (table 2).

**Comparisons at each fluticasone dose step**

Paired data were available at each fluticasone dose as follows: 500 μg, n=43; 250 μg, n=43; 100 μg, n=56; 50 μg, n=50; 0 μg, n=18 (table 5). At 500 μg, morning peak expiratory flow (PEF) was significantly higher on placebo than on simvastatin (p=0.007). At 0 μg/day, ACQ was significantly lower (p=0.057), and both prebronchodilator and postbronchodilator FEV₁ were significantly higher on simvastatin than placebo (p<0.001 and p=0.01, respectively). No other significant differences were seen.

**Table 1** Characteristics of study participants at study entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean (range)</td>
<td>45 (20–68)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Age of onset (years)†</td>
<td>14 (0–33)</td>
</tr>
<tr>
<td>Ex-smokers*</td>
<td>12 (28%)</td>
</tr>
<tr>
<td>Atopic†</td>
<td>35 (81%)</td>
</tr>
<tr>
<td>On ICS*</td>
<td>42 (98%)</td>
</tr>
<tr>
<td>On LABA*</td>
<td>17 (40%)</td>
</tr>
<tr>
<td>ICS dose (μg daily)††</td>
<td>1000 (500–1000)</td>
</tr>
<tr>
<td>ACQ</td>
<td>0.8 (0.6)</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>86 (19)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>68 (10)</td>
</tr>
<tr>
<td>FEV₁ % change postbronchodilator†</td>
<td>9 (5–15)</td>
</tr>
<tr>
<td>FENO (ppb) §</td>
<td>30.9 (25.3–37.8)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD) unless otherwise stated.
*Expressed as n (%).
†Expressed as median (IQR).
‡Beclomethasone equivalent: 1 μg beclomethasone = 1 μg budesonide = 0.5 μg fluticasone.
§Expressed as geometric mean (95% CI).

ACQ, Asthma Control Questionnaire; FENO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β-agonist.

**Figure 2** Kaplan–Meier plot showing the number of subjects without loss of control at each fluticasone dose during monthly stepwise dose reduction from 500 μg/day to 0 μg/day with simvastatin and placebo. There was no significant difference between simvastatin and placebo (p=0.404).
Taking simvastatin 40 mg at night or placebo.

Asthma

Table 2 Comparison of symptoms (ACQ, ACT), quality of life (AQLQ), bronchodilator use, lung function (PEF and FEV1), airway hyper-responsiveness (PC20AMP) and airway inflammation (FrNO and sputum cells) in all patients at 'minimum' dose while taking concomitant simvastatin 40 mg at night or placebo.

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin</th>
<th>Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACQ</td>
<td>0.3 (0.0–1.1)</td>
<td>0.7 (0.3–1.2)</td>
<td>0.171</td>
</tr>
<tr>
<td>ACT</td>
<td>22 (19–24)</td>
<td>21 (18–24)</td>
<td>0.425</td>
</tr>
<tr>
<td>AQLQ</td>
<td>6.7 (6.3–6.9)</td>
<td>6.6 (5.9–6.8)</td>
<td>0.150</td>
</tr>
<tr>
<td>Salbutamol use (puffs/24 h)</td>
<td>0 (0–0.8)</td>
<td>0.2 (0–0.8)</td>
<td>0.731</td>
</tr>
<tr>
<td>Mean morning PEF (l/min)</td>
<td>415 (110)</td>
<td>408 (107)</td>
<td>0.063</td>
</tr>
<tr>
<td>Mean evening PEF (l/min)</td>
<td>423 (112)</td>
<td>418 (108)</td>
<td>0.149</td>
</tr>
<tr>
<td>Pre-BD FEV1 (litres)</td>
<td>2.61 (0.72)</td>
<td>2.62 (0.75)</td>
<td>0.659</td>
</tr>
<tr>
<td>Post-BD FEV1 (litres)</td>
<td>2.92 (0.78)</td>
<td>2.90 (0.79)</td>
<td>0.539</td>
</tr>
<tr>
<td>PC20AMP (mg/ml)*</td>
<td>32.5 (17.8–59.7)</td>
<td>46.3 (23.9–89.7)</td>
<td>0.144</td>
</tr>
<tr>
<td>FrNO (ppb)*</td>
<td>31.7 (26.4–38.2)</td>
<td>27.3 (22.0–33.8)</td>
<td>0.098</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>9.9 (5.7–27.0)</td>
<td>22.7 (13.4–37.8)</td>
<td>0.047</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>23.6 (9.1–47.4)</td>
<td>14.5 (6.3–27.5)</td>
<td>0.030</td>
</tr>
<tr>
<td>Macrophages (%)</td>
<td>33.0 (19.3–57.0)</td>
<td>36.3 (25.1–55.8)</td>
<td>0.400</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>0.7 (0.3–1.8)</td>
<td>0.7 (0.0–1.5)</td>
<td>0.429</td>
</tr>
</tbody>
</table>

Comparisons are by paired t tests (presented as mean (SD)) and Wilcoxon signed rank tests (p Values are for comparisons between simvastatin and placebo; significant values are in bold.

AHR, sputum cells and cytokines

In the subgroup who were down-titrated to 0 µg fluticasone (n=18, of whom 8 did not experience LOC), PC20AMP was similar with both simvastatin and placebo (table 4). Sputum eosinophils were significantly lower (p=0.033) and lymphocytes significantly higher (p=0.003) with simvastatin. There were no significant differences in any of the sputum mediators between simvastatin and placebo (table R3, Online repository).

DISCUSSION

This is the first study to assess the steroid-sparing effects of simvastatin in patients with eosinophilic, steroid-responsive asthma. Our principal finding was that simvastatin was not associated with a clinically important steroid-sparing effect. The ‘minimum’ steroid dose required to establish asthma control was the same whether taking simvastatin or placebo. Similarly, the dose at which LOC occurred following steroid reduction was comparable in both treatment arms, and in patients who experienced LOC in both arms, the steroid dose at which it occurred was no different.

In patients whose steroid treatment was reduced to 0 µg/day (n=18, of whom 10 lost control), simvastatin was associated with minor improvements in ACQ and FEV1 (table 3). Simultaneously, sputum eosinophils were reduced with simvastatin (from 25.4% to 9.5%, p=0.035). In all patients, when taking their ‘minimum required’ fluticasone dose, sputum eosinophils were significantly lower with simvastatin (9.9% vs 22.7%, p=0.047), despite the fact that the mean ‘minimum’ dose was almost identical (168 vs 157 µg/day). Taken together, these data suggest that although an anti-inflammatory effect may occur with simvastatin, it was insufficient to have any significant impact on steroid requirements. Our data pertaining to sputum eosinophilia are in keeping with animal-based studies, which showed reduced eosinophils after allergen challenge in statin-treated mice.

Despite a reduction in sputum eosinophils with simvastatin, there were no differences in AHR or sputum mediators (interleukin 4 (IL-4), IL-5 or eotaxin). The dissociation between changes in inflammatory cells versus AHR and symptoms has been reported with anti-IL-5 treatment. In an in vitro study of eosinophils from patients with asthma, simvastatin induces apoptosis, and lovastatin enhances phagocytic clearance of apoptotic cells. Thus the reduction in sputum eosinophils with simvastatin may result from apoptosis induction and/or increased eosinophilic clearance.

At ‘minimum required’ fluticasone dose, sputum eosinophils remained increased. Despite unresolved sputum eosinophilia, the median ACQ was 0.3 with simvastatin and 0.7 with placebo (non-significant), indicating adequate asthma control. Changes in sputum eosinophils may be out of phase with asthma control by up to 20 days. In addition, steroid withdrawal may result in ' rebound' eosinophilia. These phenomena may explain why sputum eosinophils remained elevated at 'minimum' dose, yet with relative suppression of eosinophils with simvastatin compared with placebo.

Non-eosinophilic patients were excluded so that the effect of treatment specifically on the eosinophilic phenotype could be assessed. We avoided recruiting 'all-comers' in whom treatment response is more likely to be variable. Asthma is pathologically heterogeneous, as is the response to disease-modifying treatments. Ideally clinical trials should include patients with a similar pathological phenotype. This is illustrated in studies of the anti-IL-5 antibody, mepolizumab. Whereas outcomes in unselected patients were disappointing, in later studies patients with an eosinophilic phenotype were selected and positive outcomes were achieved, indicating that matching treatment to phenotype is important. Further studies are needed to investigate the effects of statins in non-eosinophilic asthma in the light of promising outcomes in COPD.

There are only two clinical studies that have previously assessed statins in asthma. In the first small study (n=16), simvastatin was given for 4 weeks. In the second (n=54), atorvastatin (40 mg daily) was administered for 8 weeks, but regular ICS treatment was continued. Neither study demonstrated important differences between statin and placebo for symptoms, spirometry or AHR, although sputum leukotriene B4 and macrophages decreased significantly with atorvastatin.
However, there are weaknesses in their design. First, treatment duration was relatively short. In our study, length of treatment depended on when/whether a patient reached LOC, but all comparisons are by paired t tests (presented as median (IQR)).

Comparison are by paired t tests (presented as mean (SD)) and Wilcoxon signed rank tests (presented as median (IQR)).

Comparison of symptoms (ACQ, ACT), quality of life (AQLQ), bronchodilator use, lung function (PEF and FEV1) and airway inflammation (FENO) in those patients with paired measurements obtained at 500, 250, 100, 50 and 0 μg daily of inhaled fluticasone during stepwise reduction while taking concomitant simvastatin 40 mg at night or placebo.

Table 3 Measures of asthma control during stepwise reduction in ICS dose while taking simvastatin and placebo

<table>
<thead>
<tr>
<th>Fluticasone dose (µg/day)</th>
<th>Sim 500 (n = 43)</th>
<th>Placebo 250 (n = 43)</th>
<th>p Value</th>
<th>Sim 100 (n = 36)</th>
<th>Placebo 50 (n = 30)</th>
<th>p Value</th>
<th>Sim 0 (n = 18)</th>
<th>Placebo 0 (n = 18)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACQ</td>
<td>0.5 (0.0–1.2)</td>
<td>0.182 (0.5 (0.2–1.3)</td>
<td>0.003</td>
<td>0.603 (0.0–1.2)</td>
<td>0.764 (0.0–1.7)</td>
<td>0.035</td>
<td>0.4 (0.0–1.8)</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>ACT</td>
<td>0.3 (0.0–0.8)</td>
<td>0.4 (0.0–1.0)</td>
<td>0.155</td>
<td>0.5 (0.0–1.2)</td>
<td>0.7 (0.4–1.6)</td>
<td>0.12</td>
<td>1.2 (0.3–2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQLQ</td>
<td>6.7 (6.2–6.9)</td>
<td>0.339 (6.0–6.9)</td>
<td>0.088</td>
<td>0.547 (6.5–6.9)</td>
<td>0.855 (6.7–6.9)</td>
<td>0.236</td>
<td>6.7 (5.5–6.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reliever use (puffs/24 h)</td>
<td>0 (0–0.4)</td>
<td>0.407 (0–0.9)</td>
<td>0.076</td>
<td>0 (0–1.4)</td>
<td>0.339 (0–1.8)</td>
<td>0.056</td>
<td>0.1 (0–2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean morning PEF (l/min)</td>
<td>412 (119)</td>
<td>417 (124)</td>
<td>0.062</td>
<td>417 (124)</td>
<td>0.946 (412 (121)</td>
<td>0.663</td>
<td>441 (112)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean evening PEF (l/min)</td>
<td>414 (118)</td>
<td>421 (125)</td>
<td>0.001</td>
<td>421 (125)</td>
<td>0.730 (422 (119)</td>
<td>0.763</td>
<td>447 (111)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-BD FEV1 (litres)</td>
<td>2.66 (0.78)</td>
<td>0.677 (2.61 (0.78)</td>
<td>0.009</td>
<td>2.62 (0.79)</td>
<td>0.455 (2.58 (0.79)</td>
<td>0.527</td>
<td>2.79 (0.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-BD FEV1 (litres)</td>
<td>2.65 (0.77)</td>
<td>2.67 (0.78)</td>
<td>0.010</td>
<td>2.68 (0.82)</td>
<td>2.60 (0.78)</td>
<td>2.57</td>
<td>0.6 (0.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FENO (ppb)*</td>
<td>18.7 (15.9 to 22.1)</td>
<td>20.4 (16.8 to 24.8)</td>
<td>0.158</td>
<td>21.9 (17.5 to 27.3)</td>
<td>0.326 (29.3 (23.4 to 36.7)</td>
<td>0.107</td>
<td>41.7 (32.3 to 54.0)</td>
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</tbody>
</table>

Table 4 Comparison of airway hyper-responsiveness (PC20 AMP) and sputum cells at 0 μg fluticasone daily in the subgroup (n=18) reaching this dose after stepwise reduction while taking concomitant simvastatin 40 mg at night or placebo

<table>
<thead>
<tr>
<th>Fluticasone dose (µg/day)</th>
<th>Sim 500 (n = 43)</th>
<th>Placebo 250 (n = 43)</th>
<th>p Value</th>
<th>Sim 100 (n = 36)</th>
<th>Placebo 50 (n = 30)</th>
<th>p Value</th>
<th>Sim 0 (n = 18)</th>
<th>Placebo 0 (n = 18)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC20 AMP (mg/ml)*</td>
<td>27.4 (12.2 to 61.6)</td>
<td>47.6 (16.7 to 135.7)</td>
<td>0.014</td>
<td>25.4 (15.2–48.2)</td>
<td>0.033</td>
<td>23.6</td>
<td>19.0 (29.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>9.5 (5.7–31.1)</td>
<td>20.2 (11.3–51.3)</td>
<td>0.037</td>
<td>16.1 (4.9–35.5)</td>
<td>0.145</td>
<td>19.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>34.0 (19.9–56.9)</td>
<td>3.8 (0.7–0.4)</td>
<td>0.003</td>
<td>2.8 (16.6–45.6)</td>
<td>0.215</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis of variance was performed on logarithmically transformed data. Analysed using Wilcoxon signed rank tests.

*Analysed by paired t test after logarithmic transformation and results presented as geometric mean (95% CI).

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; BD, bronchodilator; FENO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; Pla, placebo; Sim, simvastatin.

We used simvastatin at a dose of 40 mg daily. Data from several studies supported the selection of simvastatin as the trial drug. In murine models, simvastatin reduces eosinophil inflammation and AHR, while in vitro human studies indicate that simvastatin induces eosinophil apoptosis and inhibits proliferation of airway smooth muscle cells. The choice of dose (40 mg daily) was based on data demonstrating anti-inflammatory effects (reduced serum IL-6, IL-8 and monocytic chemotactrant protein-1) at this dose. We cannot exclude that lack of clinical effect may be because the dose of simvastatin was too low.

A subgroup of patients had no LOC after ICS withdrawal: this occurred in 8 (19%) in both treatment arms, in 6 (14%) with simvastatin and 3 (7%) with placebo; their ‘minimum’ ICS dose requirement was 0 μg/day. Arguably, the inclusion of patients with mild asthma may have reduced the potential to show a treatment effect. However, at the study outset, of 45 patients who were enrolled, 42 (92%) were taking regular ICS and 17 (40%) were also taking a regular long-acting β-agonist. Moreover, after ICS withdrawal in Phase 1, 36 (84%) demonstrated LOC, indicating that they were ‘steroid requiring’. The duration of each step during ICS dose reduction was 1 month. If the interval between adjustments had been longer, LOC may have occurred in these patients, and consequently the calculated ‘minimum dose’ requirement would have been higher. Reassuringly, a posthoc analysis of patients who experienced LOC during ICS reduction (n=56, 84%) revealed no significant difference between simvastatin and placebo (Online repository: figure R1).

In conclusion, our results suggest that statin treatment is unlikely to be beneficial in managing specifically eosinophilic asthma. No clinically important steroid-sparing effects were demonstrated. In the absence of steroid, simvastatin is associated with minor improvements in symptoms and lung function, together with reduced sputum eosinophilis, the relevance of which is unclear. Given the apparent benefits of statin treatment reported in epidemiological studies of COPD, it may be that in other airways disease phenotypes, statins may have a role.
Asthma

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Lower South Island Ethics Committee, New Zealand.

Contributors DCC conducted the study and was responsible for analysing the data and writing the manuscript; JDC, RP and AW provided technical support; DRT designed the study, supervised its conduct and wrote the manuscript.

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