Author’s response to reviews

Title: Effects of short-term treatment with atorvastatin in smokers with asthma - a randomized controlled trial

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Author’s response to reviews:

Dear Dr Tim Shipley

Title: Effects of short-term treatment with atorvastatin in smokers with asthma – a randomized controlled trial

Thank you for giving us the opportunity to revise our manuscript in the light of the reviewers’ helpful comments. Please find below a point-by-point response to each individual comment raised by each Reviewer. The changes to the text of the revised manuscript are highlighted in yellow.

Reviewer’s report #1

Reviewer: Nicholas Kenyon

Major comments:

1. Some rationale as to why this statin and dose was chosen for the trial. Does the type of statin make a difference?

Response

A rationale for the use of atorvastatin in now included in the introduction (page 5):

‘Atorvastatin was chosen because of its favourable anti-inflammatory properties 1-3 and evidence of clinical benefit at the dose of 40 mg daily in rheumatoid arthritis 2’.
2. Some of the references refer to animal models in which statins were shown to decrease the development of airway inflammation. This study is designed to address treatment of established airway inflammation at 4 weeks. Is this a long enough time period? The authors could further compare their study design to recent manuscripts suggesting effects on remodeling, including Wright et al. Am J Respir Crit Care Med Vol 183. pp 50–58, 2011. Zeki et al. Translational Research 2010;156: 335–349, Ou et al. (2009) 14, 734–745. Is a longer study worth it in the authors’ opinion?

Response

It is difficult to be sure that 4 wks treatment is a long enough period to suppress airway inflammation in asthma. In support of an anti-inflammatory effect during this time period is provided by the observations that statins reduce airway inflammation within a 24 hrs following LPS challenge in man4 and within 14 days in acute lung injury5. The discussion has been revised in relation to this point (page 13):

‘The short duration of treatment with atorvastatin may have missed an effect on clinical or inflammatory outcomes’.

We agree with the reviewer that studies involving the administration of statins for a prolonged period of time are indicated in view of potential effects on indices if airway remodelling. The discussion has been revised to emphasise this point (page 13):

‘Statins have an inhibitory effect on human airway smooth muscle cell proliferation6 and indices of airway remodelling7-9. It is possible that the administration of atorvastatin therapy for a longer duration of time may improve outcome measures of airway remodelling in asthma’.

3. The use of LABAs in the atorvastatin group was less than the placebo group. Was this statistically significant? Were any of the variables significantly different at baseline? While questionnaire scores are not significantly different at baseline, it could be argued that this LABA difference may have an effect on asthma control?

Response

There was no significant difference in the use of LABAs in the atorvastatin group compared to the placebo group. None of the other variables was significantly different at baseline. The following sentence has been added to the discussion (page 13):

‘Secondly, while questionnaire scores were not significantly different at baseline, it is possible that the slight difference in the proportion of participants taking LABA prior to screening may have had an effect on subsequent measurements of asthma control’.

Minor comment:
1. IL17 is discussed as a potential mechanism in the discussion. Was this measured in sputum or serum?

Response
Unfortunately IL 17 was not measured in either sputum or serum samples

2. On page 8: patient substitution of PEF values for missing PEF data raises possibility of increased variability in PEF measures/analysis. Perhaps authors can comment on this in the discussion as a limitation.

Response
We have added the following sentence to the discussion (page 13):

‘If fewer than three days of data were recorded during the seven days immediately preceding each study visit, patient diary entries for morning PEF were substituted in place of the missing values, which raises the possibility of increased variability in PEF measurements. However this procedure was performed in a minority of PEF measurements used in the analysis and is unlikely to have influenced the PEF result’.

3. The authors need to briefly explain the absolute score and significance cut offs for the quality of life scores surveys.

Response
We have added the following sentence to the methods section (pages 6-7):

‘The total AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. A change in score of 0.5 is the smallest change that is considered clinically important’.

Reviewer's report #2
Reviewer: Yoshihiko Chiba

Comments
1. (Page 5, line 14) It is better to provide information of some medications known to interact with statin for readers.

Response
The following sentence has been added to the methods section (page 5)

‘medications known to interact with statins such as antifungal agents, macrolide antibiotics, , cyclosporin, gemfibrozil, verapamil and amiodarone’

2. The reviewer does not make sense the number of patients at the beginning of the study. 131 (page 8, line 4 from the bottom) or 286 (Fig. 1)? Which is correct?
Response
The text has been revised as follows (page 9):

‘Of the 286 subjects contacted, 131 volunteers were consented and 71 were randomized to either the atorvastatin treatment group (n=36) or the placebo group (n=35) (Figure 1)’.  

3. (Page 10, line 14) The reviewer could not find Fig. 4.

Response
Table 4 has been added to the manuscript (page 22)

4. The authors should address the reason why the statin treatment improved the QOL without affecting lung function.

Response
The mechanism(s) by which atorvastatin treatment improved QOL without affecting lung function can not be determined from the data collected. Clinically important improvements in the AQLQ score were observed in a trial comparing different formulations of inhaled beclometasone10 and in a double-blind sham-controlled trial of bronchial thermoplasty11 while in both studies conventional clinical indices of lung function and asthma control were similar. 

We believe that we have adequately addressed the Reviewers comments and that the revised manuscript has been improved in the light of these changes. We hope that it will now be considered suitable for publication in BMC Pulmonary Medicine

Yours sincerely

Neil C Thomson