Author's response to reviews

Title: Emerging therapies for severe asthma

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Author's response to reviews: see over
Dear Robin

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

**Editor’s comments:**

1. Abstract: The abstract is a vital part of the article, to encourage browsing readers to download the full text, so must be engaging and informative. The current abstract generally fulfil these criteria, however, I have suggested some minor revisions to improve the structure and flow.

   **Response:** Thank you for your helpful comments which have been included in the revised text.

2. Introduction: BMC Medicine has a general medical audience, so researchers and clinicians from many different specialisations may read your article. Therefore the ?basics? of your review topic should be clearly introduced at the start of the article. To that end, please start with 2-3 more general sentences about asthma. In addition, referee 2 has raised some concern about the way that resistant asthma is defined, which we would like you to address here. Finally, in your final sentence, you discuss your aims for the review, but you make no mention of the genotype/phenotype effects that you include in the abstract, please modify this as appropriate.

   **Response:** General sentences about asthma added. To prevent any confusion in terminology we have changed the term "treatment resistant" asthma to severe asthma. The final sentence has been modified as requested.

3. Main text-Biological agents
   This section would benefit from a brief introductory paragraph summarising the agents you intend to cover. Referee 2 has commented on a number of points in this section, asking for modification and inclusion of some further information, particularly about anti-CD25 mAbs. Finally, I think it would be very useful to include a brief glossary for this section reminding the readers what the different interleukins do. This can be added as a text box, and I have highlighted the terms I thought you should include.

   **Response:**
   A brief introductory paragraph has been added that summarises the agents to covered in the review.
   We have included reference to the use of daclizumab, an anti-CD25 antibody, in patients with moderate to severe asthma.
   Brief glossary reminding the readers what the different interleukins do has been added as a text box.

4. Main text-New inhaled long-acting bronchodilators and corticosteroids. Please include one or two sentences to introduce this section.

   **Response:** Short introduction added to this section
5. Main text-Factors influencing the response to novel therapies
   You promise a discussion of genotypic/phenotypic effects on therapy, but really only very briefly light on this topic in the text. Please try to expand this section. I have suggested some points that you might consider to help you accomplish this.

   **Response:** We have expanded this section as suggested.

6. Figures: If you use previously published figures, it is your responsibility to gain permission from the copyright holder (usually the publisher) to reproduce the figure.

   **Response:** Permission sought

7. Conclusions: Please include a summary and future directions section just before the conclusions.

   **Response:** Summary and future directions section added

**Reviewer #1**

I have only one request as a minor revision: could we see the baseline AQLQ scores in figure 3 to reassure us that no correction for baseline values is required?

**Response:** The AQLQ scores in the figure 3 are absolute values. The figure includes baseline AQLQ scores. The legend has been revised to make this point clearer.

**Reviewer #2**

1. I am a little worried about the use of the term "treatment resistant" asthma without a clear definition. In principle, the definition of "difficult/therapy-resistant asthma" (as used by the ERS taskforce in 1999) is too broad. This term was used to describe patients with poorly controlled asthma despite prescription of a reasonable dose of ICS and included not only patients with truly severe asthma, but also those in whom asthma management is difficult due to poor adherence, incorrect inhaler technique, psychological problems and co morbidities. More recent definition of chronic severe asthma distinguished patients with ?severe asthma? from those with ?difficult to treat asthma?, the latter presenting with uncontrolled asthma due to other factors than asthma itself, and therefore not being candidates for immune suppressive or innovative therapies

   **Response:** To prevent any confusion in terminology we have changed the term "treatment resistant" asthma to severe asthma.

2. The ability of omalizumab for a significant systemic steroid sparing effect remains to be established, given that omalizumab was studied mainly as add-on therapy in moderate and severe asthma patients not routinely receiving oral corticosteroids. To the best of our
knowledge, only one study to date has specifically investigated the effectiveness of omalizumab in allergic patients with steroid-dependent asthma (Domingo and coll. Curr Med Res Opin 2011;27:45?53).

Response: In the article we do not claim that omalizumab has a significant systemic steroid sparing effect. The text states the following: ‘In patients with allergic asthma, omalizumab treatment improves symptoms and reduces exacerbations[14, 15]. We believe that the two references support this statement.

3. I would like to see mentioned of anti-CD25 mAbs

Response: Thank you for this suggestion. We have included reference to the use of daclizumab, an anti-CD25 antibody, in patients with moderate to severe asthma.

4. I would tone down the role of bronchial thermoplasty (BT) in chronic severe asthma. Also, figure 3 shows a very marginal (and probably clinically irrelevant) role for BT. I would deleted it out.

Response: We have revised this section to ‘tone down’ the role of bronchial thermoplasty. We believe that figure 3 should be retained to allow readers to make their own opinion on the clinical relevance of the changes in asthma quality of life.

We believe that we have adequately addressed your comments and those of the reviewers. 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 Medicine.

Yours sincerely

Neil C Thomson