Format for ANSWERING REVIEWERS

March 15, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16776-review.doc).

Title: Clinical asthma phenotyping: A trial for bridging gaps in asthma management

Author: Magdy Mohamed Zedan, Wafaa Nabil Laimon, Amal Mohamed Osman, Mohamed Magdy Zedan

Name of Journal: World Journal of Clinical Pediatrics

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The manuscript has been improved according to the suggestions of reviewers:

[A] Reviewer 1 comment (Reviewer's code: 00646232)
I read with interest this article about (Clinical Asthma Phenotyping; a Trial for Bridging Gaps in Asthma Management).The topic is relatively new and there are few data about the topic of the study especially in children and I think there are very few articles in the same field. I strongly recommend acceptance of this article. However, just I recommend that the author is be better do a table demonstrating the various asthma phenotypes with its genetic basis, pathological basis, lung functions, clinical presentation as well as its treatment.
Answer:
Thank you very much for your appreciation and kind support
According to your valuable recommendation, Table 1 was added in a trial to correlate some proposed clinical asthma phenotypes with underlying genetic, biological, molecular levels to their therapeutic responses.
[B] Reviewer 2 comments (Reviewer's code: 00646241)
1- Comment no. 1:
In their paper, "Clinical Asthma Phenotyping; a Trial for Bridging Gaps in Asthma Management" the author presents an informative overview covering several aspects that may be relevant for a possible subclassification of asthma, presenting a limited review of the literature in the field. The work contains most of the information necessary, however several details should be clarified or added. Asthma may be subclassified by aspects of clinical presentation, molecular genetic findings – that first have to be defined – and by certain laboratory findings, e.g. sputum analysis.

Answer to comment no.1:
It is well known that many trials for asthma phenotyping have been postulated following

both biased and unbiased approaches. However, asthma phenotyping is still a wide sophisticated subject with great heterogeneity. Thus, our aim was not to collect a lot of details but to highlight the main levels of asthma classifications in a trial to bridge the gaps in asthma therapy.
Further, we have mentioned several aspects of asthma sub-classification

- As regard the clinical presentation, we mentioned:
  "Different studies suggest phenotypic classification of asthma depending on clinical basis. These phenotypes include allergic and non allergic asthma. Other phenotypes defined by clinical or physiological categories (i.e. severity, age at onset, and chronic airway obstruction), by asthma triggers (i.e. viral, exercise, occupational allergens, or irritants), or their course (i.e. early transient/persistent/late onset wheeze) have also been proposed [8]. Other asthma phenotypes include cough variant asthma and obese asthma phenotype."

- As regard the molecular level, we mentioned
  "Despite the importance of Th2 cytokines in atopic asthma, recent data in both adults and children has challenged the concept of a Th1/Th2 imbalance and has showed an evidence of Th1 profile.
  Th2 imprint was present in only 50% of the mild asthmatics and those patients were characterized by lung eosinophils, mast cells, higher IgE levels, hyperreactive airway, higher tissue expression of Th2 cytokines and thicker subepithelial basement membrane [24, 25]. In addition, they showed a good response to inhaled corticosteroids in contrast to those without the type-2 cytokine profile"

2- <u>Comment no. 2:</u>
Asthma therapy may be stratified on the basis of such a subclassificaton, either depending on logical conclusions (asthma with predominant cough may be treated by antitussiva, or asthma with predominantly allergic features may be treated by antiallergics) – or on statistical findings. However, any such stratification should be validated by further clinical studies to achieve evidence.

Answer to comment no.2:
Thank you for your valuable notice.
Table 1 was added trying to stratify asthma therapy according to some proposed clinical asthma phenotypes in correlation with their molecular and biological backgrounds when avaiable. This included exercise induced asthma, obese asthma phenotype, early onset allergic asthma, late onset eosinophilic asthma, cough asthma phenotype, wheezy and shortness of breath phenotypes.
3- <u>Comment no. 3:</u>
In the work, several analyses or interpretations are collected, however, the evidence

levels of the findings are not given, results from numerous studies ranging from molecular genetics to clinical presentations, are just collected, and clear conclusions are lacking – the authors do not propose algorithms for appropriate therapy stratifications, nor do they develop a strategy to gain evidence for such an algorithm. Any of their information would be more clearly understandible if additionally presented in form of a table.

Answer to comment no.3:

- There have been previous attempts for asthma therapy stratifications. However, some of them have been disappointing e.g. anti-IL-5 therapy. Thus, there are still difficulties in translating the clinical findings to the therapeutic settings. Large-population meticulous unbiased studies are required in order to approach a proper asthma therapy algorithm.
- Table 2 was added for more clarification of the proposed clinical asthma phenotyping.

4- Comment no. 4:

Besides, some language polishing seems still necessary (see below).Thus the paper should be substantially improved to be published. Some examples of the numerous language problems:p.1Instead ofThis article reviews different published work in terms of unbiased approacheswriteThis article reviews different published works in terms of unbiased approachesp.2.Instead ofThe fact that there was a group of asthmatic patients with variable presentations who did not respondwriteThe fact that there is a group of asthmatic patients with variable presentations who do not respondp.3.Instead ofthese different phenotypes of asthma still have diverse underlying biologic disease processes in each individual writethese different phenotypes of asthma are based on diverse underlying biologic disease processes in each individual and so forth.

Answer to comment no.4:

The paper has been accurately revised and the mentioned language polishing has been corrected in the manuscript