Author's response to reviews

Title: Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses

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Author's response to reviews: see over
Dear Sir/Madam,

Enclosed please find our revised paper *Double-blind placebo-controlled food challenges in children with alleged cow’s milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses.*

We have revised our paper according to the reviewers’ comments. Please see our detailed reactions below.

Reviewer 1

*Major compulsory revisions.*

1) It is correct that patients were prospectively enrolled as was mentioned in the *Methods* section of the manuscript. We agree with Reviewer 1 that it is better to mention the construction of two age groups in the results section. We have changed this in the manuscript.

2) As requested by Reviewer 1, we have added information regarding follow-up duration in the Results section *reintroduction of cow’s milk.* The two DBPCFC negative patients with a follow-up of less than 1 month (unable to contact by telephone and no information on reintroduction in medical file) are now excluded from the calculation of mean and range of follow-up duration.

3) We agree with Reviewer 1 that the two patients with reaction to placebo who were interpreted by their treating physician as ‘exchanged test feedings’ should not be included in the determination of the cumulative distribution of MEDs in our study population (figure 2 / old figure 1), since this would not add to the reliability of our MED data. These patients are also removed from table 4.

4) As requested by Reviewer 1, we have made it clearer in the *Discussion* section that our 0-12 months group is not really comparable to any of the groups published in the literature.

5) We agree with Reviewer 1 that it is better to use the population MED distribution for population risk assessment purposes only, not for assessment in individual patients. The statement concerning the stability of the individual MED is indeed derived from a Dutch paper referred to in the *Discussion* section, however is not appropriately accounted for in this reference paper. This remark is added in our *Discussion* section.

6) We have added a reference with more reliable data on development of tolerance to cow’s milk protein. We have also made clearer that the assumption that higher MEDs might result in faster tolerance development is only an interesting hypothesis. Further studies are needed to confirm or reject this.

*Minor essential revisions.*

7) Although the physical examination by the physician was performed 20 minutes after the last test dose, the children were observed clinically at least until 1 hour after the last test dose. This is added to the information in table 1.

8) The reviewer is understandably confused by the number of patients mentioned in table 4 with regard to the positive DBPCFC’s mentioned in the text. 12 patients had acute reactions, 11 children had both acute and late reactions. Additionally 2
patients had an acute reaction to placebo feeding, which were interpreted by the treating physician as a positive test with exchange of feedings. These were included in table 4, which adds up to 25 patients in total. However, in the revised manuscript, we have removed these two patients from the MED analysis and have therefore also removed these 2 patients from table 4 (see also point 3).

9) We indeed have used ‘MED’ in different combinations throughout the manuscript; it has now been made more consistent. We have also added a paragraph in the Methods section explaining the method in more detail (also in response to reviewer 2), and added an extra sentence to the Discussion section.

10) The wrong table number is corrected.

11) The remark concerning the reference of Schade et al. (old reference 23) has been changed.

12) After the last test dose of 1620 mg, the patients continued their previous cow’s milk free diet until one week after the second day of the DBPCFC. Therefore they did not receive more cow’s milk than the dose given during the test before the reaction appeared. It is now described more clearly in the methods section that the patients continued their cow’s milk free diet until their visit to the outpatient clinic at least one week after the second test day. In table 4, patients are now sorted by eliciting dose of symptoms instead of by patient numbers.

Reviewer 2

Major compulsory revisions
1) The additional information requested by Reviewer 2 has been added to table 2.
2) We have now explained the concept of using cumulative distribution curves in more detail in the Methods Section of the manuscript. We use cumulative distributions because this allows comparison of datasets that are of different size. For instance in the present study the infant population consists of 14 individuals whereas there are seven individuals in the population of children older than 12 months. By presenting the number of new individual MEDs accumulating at each dose as a probability between 0 and 100% of the population, both populations are expressed on the same scale. We have added a graph showing the number of individual data per MED of our study populations after table 4 to show the distribution within the population. We feel that when adding these data to the cumulative distributions of figure 2 (former figure 1) this will not add clarity.

Minor essential revisions
1) Please see point 6 of Reviewer 3.
2) The additional information requested by Reviewer 2 has been added to the Methods section.
3) Table 4 has been regrouped by eliciting dose instead of patient number.

Discretionary revisions
1) The additional information requested by Reviewer 2 has been added to figure 2 (old figure 1) and table 4.
2) We agree that the finding that infants tolerate larger amounts of milk than older children deserves more discussion. We have added this to the Discussion section.
3) In retrospect, it would have been interesting to obtain the IgE levels in our patients. However, this information is not available in our patients, because determination of sIgE is not part of the Dutch guideline.
Reviewer 3

Minor essential revisions.

1) Reviewer 3 comments that it is of interest to know whether the clinical presentation of the patients with swelling, urticaria and erythematous exanthema (Table 2), could be reproduced by the oral challenges as outlined in Table 4. We have addressed this issue in the Discussion section of the manuscript.

2) The second remark of this reviewer concerns the patients with an acute and late reaction after the test. It was not stated clearly in the manuscript that patients were instructed to continue a cow’s milk free diet until at least 1 week after the second test day. Patients were only instructed to introduce cow’s milk protein after a negative DBPCFC. If patients had a late reaction at home, this was a reaction to the feeding given during the test. This is now described more clearly in the Methods section of the manuscript.

3) Reviewer 3 suggests to use a more recent reference concerning the prevalence of CMA. The reference mentioned by the reviewer (Gupta RS et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011;128;e9) indicates a prevalence of CMA in 1.7% of all children and a prevalence of 2% in young children. These percentages are similar to the prevalence of 2-3% in young children mentioned in our manuscript. The article of Gupta et al. doesn’t describe the percentage of children with symptoms suggestive of CMA, therefore, we also added another recent reference (Rona RJ et al. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 2007 Sep;120(3):638-46.)

4) Reviewer 3 also suggests a more recent reference to replace older references such as reference 5. We have replaced some older references with the reference suggested (Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 2010;126:s1-58).

5) We have added the reference of Vlieg-Boerstra BJ et al. (Placebo reactions in double-blind, placebo-controlled food challenges in children. Allergy 2007;62:905-12) regarding positive placebo reactions as suggested by this reviewer. We have added the placebo-induced reactions to the Results section reintroduction of cow’s milk. Symptoms that led to re-elimination are also mentioned in this section.

6) Reviewer 3 suggests including a summation of the experience of the Dutch medical community with food allergy and DBPCFC’s in the introduction. However, reviewer 2 suggests the introduction could be more concise. We have therefore chosen not to change the level of background information in the introduction.

It is our pleasure to offer you our revised manuscript. We thank you in advance for your time and consideration.

Sincerely yours,

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