Reviewer's report

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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Reviewer: C M Frank Kneepkens

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This is an interesting study which suggests that DBPCFCs indeed are superior to open challenges even in infants, and which shows that proper investigation can diminish the unjust use of hypoallergenic formula – although some parents seem to require yet more solid arguments to be convinced. There are, however, several points that need clarification.

Major compulsory revisions

1. Although it is presented as a prospective study, the presentation of the results suggests that it rather is a study which may have been prospective in the inclusion of patients, but essentially retrospective, as all data seems to have been brought together only after conclusion of the inclusion period. This would explain the huge differences in follow-up timing as well as for instance the somewhat embarrassing finding that ‘maybe’ in some cases placebo and verum might have been switched. Maybe the authors want to comment.

In addition, this could mean that the construction of two age groups (0-12 and >12 months) was performed after the first analysis of the results. In that case, I believe it should not appear in the methods section, but be confined to the results.

2. One of the strong points of the study is the long-term follow-up on diet changes, although it is weakened in its turn by solely relying on telephone interviews with the parents. According to the methods section, the parents were contacted ‘several months’ later. Although the median follow-up of 10 months, which only appears in Table 1, is more than adequate, Table 1 also mentions a minimum follow-up of 0 months, which is of course no follow-up at all. I would suggest the authors to adopt a minimum follow-up period of at least 3 or 4 months in order to get rid of useless data.

3. I object to the decision with regard to the two DBPCFCs with outcomes (acute reactions to placebo) which are not to the liking of the authors, and therefore are reversed. Even when an accidental exchange of the two trial feedings is the more likely cause, they are registered as reactions to placebo, and should remain so. In case of doubt, studies should be repeated. Otherwise there would not remain any solid ground for performing DBPCFCs at all.
4. As far as MED is concerned, the differences in patient groups and study set-up between the present study and those from the literature (and inbetween the latter) (Table 5, Figure 1) are huge and comparison therefore is difficult. This may be stressed more in the discussion (while for instance the remark that the Bahler group ‘is somewhat younger’ than that of the present study – 3.1 vs. 4.1 years – will not survive statistical analysis). It should especially made more clear that the 0-12 months group is incomparable to any of the other groups.

5. On page 12, last 10 lines, references are made to a Dutch paper which would show that individual MEDs remain stable over time. This is, however, an opinion paper and this statement is not appropriately accounted for in the paper. It appears to be a loose reference to a review by dr Toit et al in Arch Dis Child 2010;95:134-44, where the authors – as it were casually – say, referring to the variation in reactions to the various cow’s milk proteins: “These characteristics may account for the variability [...] in the same patient over time.” To me this seems not enough to corroborate the statement in the present paper. When the authors have no further proof of this stability, it also questions the usefulness of the MED – but the authors may be able to give further elucidation.

6. As for the 75% one-year tolerance score form the same reference, I don’t think this paper gives any reference as a proof. The only data I am aware of report a maximum tolerance percentage of 56% at 1 year and even appreciably less when only IgE-mediated allergy is concerned. Please find better references that this one. Finally, because non-IgE-mediated cow’s milk allergy is known to disappear faster than the IgE-mediated version, I do not think it is wise to end with the tentative conclusion that higher MEDs might result in faster tolerance development in a study that does not discriminate between those two forms of cow’s milk allergy. It may well be, though, that non-IgE allergy indeed asks for higher amounts of CMP in order to lead to symptoms.

Minor essential revisions

7. The DBPCFC protocol in Table 1 (which is not really an algorithm) seems to suggest that the children stayed in the ward only 20 minutes after the last dose was consumed. I suppose there was a longer observation period. Please explain.

8. I am not sure all numbers add up adequately. According to the DBPCFC results on page 8, 12 of the children who tested positive had acute reactions and 11 both acute and late reactions. The MED analysis on page 9, however, mentions 25 children with acute reactions. There may be other miscalculations as well.

9. I am not sure I fully grasp the concept of ‘population MED’ (page 9), ‘cumulative MED distribution’and ‘population MED distribution’ (page 11), and ‘MED distribution’ (conclusion, page 13). Please elaborate.


11. The discussion stresses the importance of looking for late reactions, which I
agree with. However, I don't believe the study of Schade et al (ref 23), which is presented as an argument, can be used to that extent. Please remove this remark.

12. Table 4: I find the CMP column confusing. Obviously, the late reactions group received far more than 1620 mg before the adverse reaction appeared. I would prefer not mentioning any CMP amount; if this is available, days after challenge would give more insight. For the acute reactions group, I would prefer to provide the cumulative amount of CMP. By the way: two children were having constipation as the sole symptom of allergy. How solid are those data?

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.