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: YAEL Y, LEVY

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This important study highlights the beneficial role of oral challenges in preventing unnecessary elimination diets in infants and children with alleged milk allergy, and establishes the minimum eliciting dose for milk induced adverse effects in these patients. This is relevant for all pediatricians who monitor infants' nutrition and growth.

Minor Essential Revisions

1. Background lines1-3, "The symptoms and signs...are diverse, non specific...": This statement is true only for non IgE mediated CMA, since the diagnosis of IgE mediated CMA can be easily made on the basis of immediate hypersensitivity reaction with a combination of urticaria/angioedema, vomiting and/or respiratory tract involvement. Indeed, only a minority of the study patients presented with urticaria, swelling or respiratory tract involvement, compared to GI tract involvement such as diarrhea, bloody stool and colic, or excessive crying and feeding problems (Table 2). It is of interest to know if 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. These points should be discussed, since it emphasizes the fact that most of the patients in whom the diagnosis was excluded were those with suspected non IgE mediated CMA (or late reactors as mentioned in the Conclusion section).

2. Table 3 reports 11 patients with acute and late reaction after verum feeding: were the patients instructed to continue milk feeding at home after an acute reaction (even though it was not known if it was to the placebo or verum feeding?

3. Background, second paragraph, lines 1-2 "The real prevalence of CMA...between 5-15% of infants show symptoms...": These numbers are over-estimation, I suggest a recent article in which CMA was reported in 1.7% of the 38,480 children who participated in the survey (Gupta RS et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011;128;e9).

4. I also suggest a more recent article to replace older references such as reference 5: 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. The authors report that 22% of the children in whom milk allergy was excluded
reacted to the placebo feeding alone. In this aspect, another study can be added in which positive placebo challenges were documented in 12.9% of the DBPCFC to several foods in children: 5/43 for milk, 4 reacted to placebo alone (Vlieg-Boerstra BJ et al. Placebo reactions in double-blind, placebo-controlled food challenges in children. Allergy 2007;62:905-12). Immediate perioral rash or exacerbation of facial eczema in response to any feeding may be found in children with atopic dermatitis, and in my opinion is not specific and is not an indication for elimination of the food. Of interest is the fact that in five out of 14 children with late reaction after placebo alone, reintroduction of milk stopped with medical advice (Table 3). It will be interesting to know what the clinical presentation of the placebo induced reactions was, and what led to the re-elimination of milk from the diet: it is known that the symptoms of eosinophilic esophagitis or milk induced enteropathy may reappear only after prolonged milk exposure of weeks.

6. I believe that references from the 80’s (7,13) can be replaced by newer ones. In addition, many references are in Dutch (I could not find full texts in English). This makes it difficult for many international readers to fully appreciate the article. In view of the substantial experience of the Dutch medical community with food allergy in general, and specifically double-blind placebo-controlled food challenges, I suggest that the first part of the introduction will include a summation of this experience, and the specific references will be mentioned later on as necessary.

**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