

PRO AND CON

The role of hydrolysates for atopy prevention – con

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With increasing speculation regarding early life 'Determinants of Health and Disease' (the DoHAD model), infant feeding practices continue to be investigated as potentially modifiable risk factors for the prevention of allergic disease, including food allergy, which appears to reflect a second wave of allergic disease (1, 2). One of the key potential interventions of interest is the use of modified infant formulas – especially partially (PHF) and extensively hydrolysed cow's milk formula (EHF) – which have been hypothesized to play a role in the prevention of early childhood allergic disease. Intense expectations from families with a history of allergy seeking readily available primary prevention interventions have been responded to by the industry with the development of a range of 'allergy prevention' formulae. Furthermore, peak expert bodies have felt the need to provide recommendations regarding the use of formula for the prevention of allergies. We argue here that although the well-meaning intent of these interested parties is understandable, expert allergy guidelines and parental expectations have leapt ahead of a solid evidence base. In the absence of robust scientific evidence, we do not believe that the use of partially and extensively hydrolysed formula in infancy can be currently recommended for the prevention of childhood allergic diseases.

Current infant feeding guidelines in Europe (3), the USA (4) and Australia (5) all recommend that hydrolysed formula can be considered as primary prevention therapy for allergic disease. These guidelines have been informed by the Cochrane review, the last update of which occurred in 2009 (6). This review supports the use of hydrolysed formula for the prevention of allergy especially in high-risk infants who are unable to be completely breastfed although the authors themselves recommend further larger trials because of the methodological concerns and inconsistency in the findings of the studies included in the review. It should be noted that the findings of this review are heavily influenced by the reported benefits of PHF during the first 6 yr of life demonstrated by the largest study of the review, the GINI study. We have recently demonstrated that the Cochrane review suffers from small-study publication bias (scarcity of small negative studies) (7) and thus is likely to have overestimated the beneficial effect of PHF. Since the last update of this review, new evidence from a large intervention trial of high-risk infants (the Melbourne Atopic Cohort Study) has emerged challenging the effectiveness of PHF (8). Additionally, while the GINI study outcomes up until the 6-yr follow-up were promising, subsequent results have shown little evidence of an ongoing preventive effect between the ages of 7 and 10 yr (9). These more recent findings have also not yet been incorporated into the Cochrane review (6).

GINI and MACS are the two largest trials conducted to evaluate the effectiveness of PHF, and both were industry

supported through the provision of formulae. Interestingly, although there is significant debate around the role of PHF for the prevention of allergic disease (10, 11), both show similar results (12) when the findings of the intention to treat analysis (ITT) are compared (Table 1). Although both have substantial strengths, each has limitations. As it would be unethical to mandate one type of feeding – breastfeeding exclusively or fully over complementary formula feeding – it is not surprising that both studies are complicated by the impact of parental choice during the feeding intervention. Irrespective of the strengths and limitations of each study, even in the best-case scenario, the number of high-risk children who would need to be fed with partially hydrolysed formula to prevent one child from developing allergic disease in the first year of life is as high as 80 (13) provided infant feeding patterns in GINI were replicated.

GINI results differ from the MACS only by per protocol (PP) analysis and even then only in relation to eczema outcomes (Table 1). Neither GINI nor MACS demonstrated a protective effect of partially hydrolysed whey formula (pHWF) on childhood asthma or allergic rhinitis outcomes in either PP or ITT analysis. Manuscripts from the GINI study have previously focused on the use of the PP analysis rather than ITT analysis to highlight their findings. This is problematic as it is well recognized that ITT is the preferred analysis as it maintains the benefit of randomization and reduces the risk of bias affecting the study results (14). The absence of effect seen in the ITT analysis, but the significant protective effect observed by PP analysis in GINI, suggests that this effect may be due to differential attrition in GINI by the factors related to allergic outcomes. This potential bias is supported by the higher rate of loss to follow-up of children who had eczema in early life from the pHWF group (41.7%) than from the cow's milk formula group (34.4%).

Disappointingly, the findings of the MACS have been questioned by commercially interested parties over a number of methodological concerns that are refutable (15). MACS is single blinded, and it could be argued allocation was not completely concealed although it was undertaken antenatally. However, if there was an investigator bias, this would be far more concerning if the results had demonstrated a positive effect because the study was mounted to investigate the potentially protective effect of various formulas and was industry funded. Furthermore, double blinding is harder to achieve in formula trials due to significant differences in taste and palatability. It has also been suggested that the high rate of prolonged breastfeeding observed within MACS might have reduced the benefit of pHWF although this is not argued for GINI which has a similar rate of exclusive breastfeeding at 4 months – 40.2% for MACS vs. 43.1% for GINI. Given that breastfeeding is the preferential form of infant feeding for the first 4 months of life, findings from these real-life feeding

Table 1 Comparison of study characteristics and reported outcomes for MACS vs. GINI

Characteristic	MACS (8)	GINI (9, 13, 17, 18)	Comments
Study number	620 (206 and 206 in CMF and pHWF groups)	2252 (556 & 557 in CMF & pHWF groups)	
High-Risk antenatal recruitment	Yes	Yes	
Study design	Single blind	Double blind until 3 yr of age	Blinding of participants is difficult due to differing taste and smell of formulae
% Exclusively breastfeeding up to 4 months	40.2% (231/575) [†]	43.1% (889/2061)	
Compliance feeding protocol			
At 4 months	91.5% (526/575)	93% (1834/1972)	
At 6 months	88.5% (509/575)	Not reported	
At 12 months	73.7% (424/575)	Not reported	
Study participant retention			
Age 12 months	88.5% (575/620)	82.5% (1859/2252)	
Age 2 yr	88.5% (575/620)	79.8% (1798/2252)	
Age 6/7 yr	79.8% (495/620)	74.6% (1680/2252)	
Differential participation by factors that influence allergic outcomes	None	Higher loss to follow-up in pHWF group in GINI, particularly those with early life eczema	Differential loss to follow-up may result in a falsely low rate of allergies appearing in the intervention arm and overestimate the effectiveness of pHWF
Intention to treat analysis for eczema at age 1 yr	1.14 (0.75–1.75)	0.88 (0.61–1.26)*	Neither study demonstrated a significant effect of PHF. Eczema is the only outcome for which a claim to the US FDA was made with regard to formulae for the prevention of allergic disease
Per-Protocol analysis for eczema at age 1 yr	1.03 (0.55–1.93)	0.49 (0.27–0.88)	Only result where the studies show substantively different findings. The protective effect in GINI could be related to the differential attrition by early eczema

*Based on ITT analysis reported in the 2007 paper (14). Note, the percentage figures quoted in the text of this paper does not correspond with the reported value.

[†]Figure generated for this comparison. Not reported in the 2011 publication (8).

studies are generalizable to the population and globally accepted infant feeding recommendations (16).

It is interesting that most recent recommendations from GINI suggest that casein-predominant EHF might be expected to have a more profound biological effect because the formula is more extensively modified (9). However, most guidelines recommendations are based on the fact that PHF is both cheaper and more palatable than EHF and therefore should be considered in place of EHF. Certainly, in some countries, EHF can only be medically prescribed, which significantly increases costs to the healthcare system. Added to the fact that a large number of infants would require treatment for a beneficial effect, the data suggest that recommendation of modified formula as a prevention measure for allergic disease is at best premature and at worst economically questionable.

Although it could be argued that the recommendation of modified infant formula for prevention is unlikely to be directly harmful even if the evidence of the effectiveness of such formula is not robust, it is important to note the unintended consequence of reduction in breastfeeding is a tangible indirect consequence. Breastfeeding has a myriad of potential non-allergy benefits, including infection protection and increased

infant-maternal bonding even leaving aside the reduced cost of breastfeeding compared with the use of allergy prevention formulae. Further to this, it is important that we provide the best available evidence to ensure that companies are not making misleading commercial claims.

In conclusion, we believe it is currently premature to recommend hydrolysed formula for the prevention of allergic disease including eczema. We eagerly await the timely updating of the Cochrane review with inclusion of the MACS outcomes as well as the more recent GINI long-term outcomes.

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