

In summary, the GINI trial is the largest and most comprehensive multicenter randomized and double-blind study (no case report!). The results clearly demonstrate a significant and clinically meaningful reduction in eczema risk until 3 years in infants at increased risk for allergies for 2 of the 3 hydrolyzed formulae compared to cow's milk formula as control. The observational cohort and the extension of the follow-up for both cohorts provide further post hoc analyses, including the fully breastfed group.

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REFERENCES

1. Filipiak-Pittroff B, Koletzko S, Krämer U, et al. Full breastfeeding and allergies from infancy until adolescence in the GINIplus cohort. *Pediatr Allergy Immunol*. 2018;29:96-101.
2. von Berg A, Koletzko S, Gröbl A, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol*. 2003;111:533-540.
3. von Berg A, Krämer U, Link E, et al. Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course - the GINIplus study up to the age of 6 years. *Clin Exp Allergy*. 2010;40:627-636.
4. von Berg A, Koletzko S, Filipiak-Pittroff B, et al. Certain hydrolyzed formulas reduce the incidence of atopic dermatitis, but not of asthma: three year results of the GINI-Study. *J Allergy Clin Immunol*. 2007;119:718-722.
5. von Berg A, Filipiak-Pittroff B, Krämer U, et al. Preventive effect of hydrolyzed infant formulas persists until age 6: long-term results from the German Infant Nutritional Intervention Study GINI. *J Allergy Clin Immunol*. 2008;121:1442-1447.
6. von Berg A, Filipiak-Pittroff B, Krämer U, et al. Allergies in high-risk schoolchildren after early intervention with cow milk protein hydrolyzates. 10-years results from the German Infant Nutritional Intervention Study GINI. *J Allergy Clin Immunol*. 2013;131:1565-1573.
7. von Berg A, Filipiak-Pittroff B, Schulz H, et al. Allergic manifestation 15 years after early intervention with hydrolyzed formulas - the GINI Study. *Allergy*. 2016;71:210-219.
8. Koletzko S, Filipiak-Pittroff B, Heinrich J, Koletzko B, Berdel D, von Berg A. Re: hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis. *BMJ* 2016;352:i974. <http://www.bmj.com/content/352/bmj.i974/rr-0>
9. Szajewska H, Horvath A. A partially hydrolyzed 100% whey formula and the risk of eczema and any allergy: an updated meta-analysis. *World Allergy Organ J*. 2017;10:27. <https://doi.org/10.1186/s40413-017-0158-z>.
10. Koletzko B, Bauer CP, Cierpka M, et al. Ernährung und Bewegung von Säuglingen und stillenden Frauen. Aktualisierte Handlungsempfehlungen von „Gesund ins Leben – Netzwerk Junge Familie“, eine Initiative von IN FORM. *Monatsschr Kinderheilkd*. 2016;1(64):771-797. <https://doi.org/10.1007/s00112-016-0147-2>.

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Comments on Schocker et al

To the Editor,

In a very recent article on this journal, Schocker et al¹ wondered if a series of allergic persistent reaction in breast-fed newborns, showing allergy to cow's milk, should be explained by a primary sensitization to human breast milk or by a cross-reactivity with cow's milk proteins. The authors conducted an interesting study on a 29-years old adult, who experienced such allergic pattern when he was a breast-fed baby, then experienced anaphylaxis and cardioplegia during his childhood and due to the severity of his food allergy, underwent oral immunotherapy (OIT), with an adjunctive treatment with omalizumab.¹ A possible cross-reactivity between cow's and human's casein, mainly β -casein, has been suggested in this case report. While reading this article, we raised some comments about.

In a first line, it would be very interesting to initially highlight on the possible interaction between whey proteins in skim milk and

human breast milk, when cow's milk is heated (from 75 to 100°C), a process which might increase the dimension of casein micelles and the ability to be further digested.^{2,3} It is tempting to speculate that gut mucosal immunity may be involved in a non-IgE-mediated allergic reaction to these casein-derived proteins, where group 2 innate lymphoid cells should produce significant amounts of IL-5 and IL-13, thereby contributing to a type 2-mediated inflammation.⁴ Recent reports showed that β -casein is a major protein component of cow's milk and that major frequent variants in dairy herds are A1 and A2, where recent studies showed that milk containing A1 β -casein promoted intestinal inflammation and exacerbated gastrointestinal symptoms, promoting the diagnosis of a milk intolerance, aside from lactose.⁵

Several different mutations in bovine beta-casein gene have been recently discovered, leading to at least 12 genetic variants and

out of these A1 and A2 are the most common, they differ for a single aminoacid at position 67, histidine for A1 and proline for A2 and gave origin to an intriguing hypothesis of how these genetic variants lead to allergy toward beta-casein, probably because A1 variant, which is much more diffused in cow's milk for infants, generates an immune bioactive protein, called beta-casomorphin 7 (BCM7).⁶

The authors did not address also the hypothesis whether or not the subject really suffers from a milk intolerance, rather than a true cow's milk allergy. The involvement of IgEs in this kind of milk intolerance should depend on the Th2-induced response by gut mucosal type 2 lymphoid cells.^{7,8}

Furthermore, basophil responsiveness to polyclonal anti-IgEs (control) and milk allergens should show a non-IgE-mediated response, rather than an IgE-mediated allergy.

Basophil reactivity to the many milk-derived allergens should suggest, in an attempt to meet the authors' conclusions, who reported that following 6 months of omalizumab treatment, this reactivity decreased and was much more marked following twelve months of omalizumab treatment and 2 months of OIT, than an allergic IgE-mediated mechanism must explain the reported evidence.¹ Interestingly, the greatest decrease in CD63% upon allergen-challenged basophils, following 6 months of omalizumab, seems to occur for breast milk rather than cow's milk and for human rather than bovine α -lactalbumin.¹ A much keener observation of the in vitro basophil activation should suggest that these cells are very poorly responsive to polyclonal anti-IgEs and hence poorly responsive to an IgE-mediated mechanism. Taking into account that the CD63 activation threshold is usually higher than 5%-10%⁹⁻¹¹ and that a CD63 threshold $\geq 5.01\%$ gives a limited BAT sensitivity (68.18% with CI 95% 45.11%-82.26%), so giving a significant proportion of FPs, the IgE-mediated response of basophils to the polyclonal anti-IgEs actually appears very scanty respect to the non-IgE-mediated response, modeled by fMLP.¹ In this context, it might be very difficult to ascertain if the CD63 response to the many milk allergens was elicited via an IgE-mediated response rather a non-IgE-mediated one.¹² Altogether, no further or very few allergen showed a CD63 upregulated fraction of basophils higher than 5% in a dose-dependent manner.¹ The authors should ask also if the subject investigated in their case report underwent the intake of soy milk during his first months/years of life, as in this case, a possible non-IgE-mediated gastrointestinal food allergy cannot be completely excluded.^{13,14}

The basophil activation test (BAT) indicates that the IgE-mediated response may be dampened either by anergic or by hyporesponsive basophils, and in this sense, we could not be sure about the role of an active allergic reactions to cow's milk in the adult subject. If clinical data are strongly presumptive of a full-blown allergy, then the very low poor basophil IgE-mediated response might be due to the test performance.¹⁰

The paper by Schocker et al is particularly interesting, yet basophil activation test should be improved and further insights are needed to elucidate this case report.

CONFLICT OF INTEREST

The Authors state they have no conflicts of interest.

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REFERENCES

- Schocker F, Recke A, Kull S, Worm M, Jappe U. Persistent cow's milk anaphylaxis from early childhood monitored by IgE and BAT to cow's and human milk under therapy. *Pediatr Allergy Immunol*. 2018. <https://doi.org/10.1111/pai.12843>.
- Anema SG, Li Y. Association of denatured whey proteins with casein micelles in heated reconstituted skim milk and its effect on casein micelle size. *J Dairy Res*. 2003;70:73-83.
- Hodgkinson AJ, Wallace OAM, Boggs I, Broadhurst M, Prosser CG. Gastric digestion of cow and goat milk: impact of infant and young child in vitro digestion conditions. *Food Chem*. 2018;245:275-281.
- Mjösberg J, Spits H. Human innate lymphoid cells. *J Allergy Clin Immunol*. 2016;138:1265-1276.
- He M, Sun J, Jiang ZQ, Yang YX. Effects of cow's milk beta-casein variants on symptoms of milk intolerance in Chinese adults: a multicentre, randomised controlled study. *Nutr J*. 2017;16:72.
- Sodhi M, Mukesh M, Kataria RS, Mishra BP, Joshii BK. Milk proteins and human health: A1/A2 milk hypothesis. *Indian J Endocrinol Metab*. 2012;16:856.
- Bischoff SC. Mucosal allergy: role of mast cells and eosinophil granulocytes in the gut. *Baillieres Clin Gastroenterol*. 1996;10:443-459.
- Hagau N, Gherman-Ionica N, Sfichi M, Petrisor C. Threshold for basophil activation test positivity in neuromuscular blocking agents hypersensitivity reactions. *Allergy Asthma Clin Immunol*. 2013;9:42.
- Chirumbolo S. Basophil activation test in oral desensitization to cow's milk allergy. *United European Gastroenterol J*. 2016;4:714-715.
- Chirumbolo S. Major pitfalls in BAT performance may be caused by gating protocols and CD63% cut off evaluation. *Cytometry A*. 2014;85:382-385.
- Venter C, Brown T, Meyer R, et al. Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP-an international interpretation of the MAP (Milk Allergy in Primary Care) guideline. *Clin Transl Allergy*. 2017;7:26.
- Nowak-Węgrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol*. 2015;135:1114-1124.
- Kattan JD, Cocco RR, Järvinen KM. Milk and soy allergy. *Pediatr Clin North Am*. 2011;58:407-426.
- Ahn KM, Han YS, Nam SY, Park HY, Shin MY, Lee SI. Prevalence of soy protein hypersensitivity in cow's milk protein-sensitive children in Korea. *J Korean Med Sci*. 2003;18:473-477.