Journal of Allergy & Therapy
ISSN: 2155-6121

Bauer, et al., J Allergy Ther 2016, 7:6
DOI: 10.4172/2155-6121.1000244

Short Communication Open Access

High Tolerability of a Rice and Carob-Based Cereal Demonstrated in Highly Allergic Infants and Children: A Randomized Open-Food Challenge Trial

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Received date: December 06, 2016; **Accepted date:** December 23, 2016; **Published date:** December 31, 2016

Abstract

Background: Food allergy is the most common cause of atopic symptoms in early childhood. Standard care is an exclusion diet to avoid symptoms, but is associated with a risk of nutritional deficiencies. Sinlac® is a rice- and carob-based infant cereal free from major allergens, providing full nutritional support for children suffering from food allergies. Apple polyphenols (AP) have been shown to have favorable anti-allergy properties.

Methods: A randomized clinical trial (NCT01029184) based on open-label food challenges was conducted to compare the tolerability of Sinlac® cereals with or without AP, with that of well-known allergenic foods, in subjects with severe food allergy (aged 4-40 months). Study products were Sinlac®, Sinlac®AP (0.3% in matrix), wheat, potato, milk and hen's egg. The primary endpoint was a positive reaction to open-label food challenges.

Results: Of the 51 subjects randomized, 48 completed the study. Both Sinlac® and Sinlac®AP were significantly better tolerated by atopic infants than other allergenic foods: incidence of allergic reactions was 2% with Sinlac® and Sinlac®AP, versus 49% with wheat, potato, milk or hen's egg.

Conclusion: Sinlac® and Sinlac®AP are very well tolerated and offer a nutritionally balanced option for atopic infants and children. Studies are needed to assess the benefit of adding AP to low allergenic products.

Keywords: Food allergy; Infant cereals; Tolerance; Polyphenols

Introduction

Food allergy (FA) is, with atopic dermatitis, the first manifestation of allergic disease in infancy [1,2]. The prevalence of FA has drastically increased in developed countries over recent decades [3] and is currently estimated at 8% in children and 5% in adults. The most noteworthy public health impact of FA is that on the quality of life of severely affected subjects and their caregivers, which is significantly impaired by the anxiety associated with continuous allergen avoidance and the potential risk of anaphylaxis [4].

Although the standard treatment of FA, i.e., strict avoidance of the incriminated food, is known to diminish clinical symptoms, the risk of exclusion diets is a potential lack of essential nutrients. There is therefore a need for low allergenic but nutritionally adapted products for infants and young children with one or multiple FA. Sinlac® is a complete cereal that was specifically developed for the weaning period in infants and young children suffering from milk, soy and/or wheat protein allergy or hypersensitivity. It is a combination of carob and non-hydrolyzed rice proteins low in allergenicity [5,6].

Preclinical data have shown the favourable anti-allergy properties of polyphenols [7]. Furthermore, in clinical trials, apple polyphenols (AP) were effective in reducing allergic rhinitis symptoms [8,9]. Taken together, these data demonstrate a possible role for AP-enriched hypoallergenic cereals in the management of allergic diseases.

The aim of this study was to assess the tolerability of Sinlac® with or without AP, in highly allergic subjects.

Methods

Study design

This randomized, open-label, single-center clinical trial (NCT01029184) was carried out according to the relevant legal requirements, at the specialist hospital of GaiBach bei Bad Tloz, Bavaria, Germany. The study included hospitalized infants of any ethnicity, aged 4-40 months, presenting atopic symptoms and/or a positive Skin Prick Test (SPT) (>3 mm) or positive specific RAST-IgE (>0.35 KU/l) or a positive Patch Test (significant induration). During the whole duration of the study, eligible participants were hospitalized to identify their allergy independently of the clinical trial. After caregivers have provided informed consent, participants received an oligo-allergen-free diet of Althera®, turkey meat, broccoli, zucchini, and cornbread for ≥ 5 days prior to the start of the study.

The primary objective was assessment of the tolerability of Sinlac® and Sinlac®AP (study products) on one hand, and 3 major allergenic foods (Wheat, Milk, and Egg) and a low allergenic food (Potato)

(WMEP; food products) on the other. The primary endpoint was presence or absence of objective and subjective symptoms after open-label food challenges. The secondary endpoint was morbidity, assessed by the frequency of adverse events (AEs).

Food products tested during oral challenges

Sinlac® and Sinlac®AP were manufactured by Nestle (Product Technology Center Konolfingen, Switzerland), based on the commercial recipe of Sinlac®. The apple polyphenolic extract pomactiv®hfv was manufactured by Val De Vire Bioactives, France. Wheat was provided as wheat toasts, wheat noodles or wheat-based porridge, depending on the age of the child. Milk was given as commercialized cow's milk or infant formula (BEBA®, Nestle) in infants under 1 year. Potato was given either boiled or mashed. Egg was provided as sponge fingers containing hen's egg, or boiled or scrambled hen's egg.

Open-label food challenges

Study participants were randomized to one of two following open-label food challenge sequences: "Wheat/Sinlac®/Potato/Sinlac®AP/Milk/Egg" or "Wheat/Sinlac®AP/Potato/Sinlac®/Milk/Egg". They received escalating doses at 30-minute intervals, up to a maximum cumulative dose of 62 g for Sinlac® and Sinlac®AP, and 248 g, 196 mL, 190 g and 106 g for wheat, milk, potato and egg, respectively. In the event of high sensitivity or a history of anaphylaxis to one or more specific food(s) (based on SPT and/or clinical history), subjects were excluded from the corresponding food challenge(s). Objective and subjective reactions were recorded within 24 h of administration of the dose. A wash-out period of ≥ 24 hours was respected between two food challenges, and determined according to clinical constraints and reactions to the product tested. Parents were advised to exclude other allergens from the infant's diet during the study. Any medication/treatment initiated during the course of the trial was recorded on the case report form.

Statistical analysis

The primary endpoint was evaluated using McNemar's test, both for the Intention-To-Treat (ITT) and the Per-Protocol (PP) analysis, comparing 3 groups: Sinlac®, Sinlac®AP, and other food products (WMEP). Because of the multiple comparisons, differences were considered significant if P<0.017 (Bonferroni correction). The secondary endpoint was analyzed using McNemar's test on the ITT population alone.

Results

Subject's disposition flowchart is shown in Figure 1. Fifty-one subjects were randomized and 48 completed the trial. The three study dropouts were due to: upper respiratory tract infection with fever before visit 1; withdrawal of consent; withdrawal without explanation. Thirty-seven subjects did not receive all the products in the recommended sequence but were still included in the PP dataset, as the deviation was considered minor by the investigator. Baseline characteristics are detailed in Table 1.

At enrolment, all subjects had carob or rice specific IgE<0.35KU/l. On the contrary, all were sensitized to at least one of the three allergenic foods tested: 78.4%, 86.3% and 37.2% had positive IgE to cow's milk, hen's egg and wheat, respectively. Moreover, 68.6% were sensitized to more than one allergenic food and 33.3% were sensitized to cow's milk, hen's egg and wheat.

At enrollment, symptoms of atopic dermatitis were classified as mild (SCORAD <25), moderate (25<SCORAD<50) or severe (SCORAD>50) in 45.1%, 19.6% and 9.8% of subjects, respectively; 25.5% had no skin symptoms.

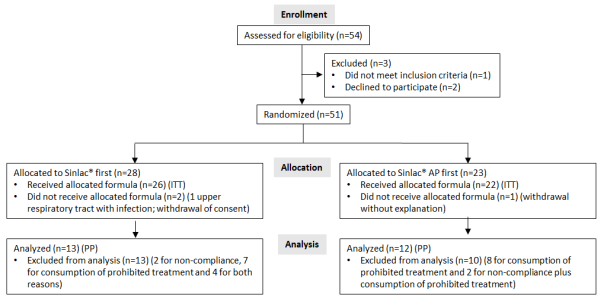

Figure 1: CONSORT Flow Diagram.

Baseline characteristics	ITT population* (N=51)	PP population** (N=25)
Gender (M/F)	35/16	15/10
Age (yrs)	1.16 1.55 2.40	1.16 1.50 2.38
Baseline SCORAD	15.5 20.3 30.0	19.9 23.15 30.1
Study completion (yes/no) %	94/6	100/0

* All randomized subjects who consumed study and/or food products at least once.

** All randomized subjects who adhered to protocol requirements with no major violation (including <50% of study product/food absorbed during the food challenge despite no adverse reactions, and/or consumption of prohibited treatment during the study period).

Table 1: Baseline characteristics of the ITT and PP populations.

During the study period, 25 subjects reported a total of 35 allergic reactions. Sinlac® and Sinlac®AP caused eczema symptoms in 2 different subjects (although both had negative results for carob and rice specific IgE). The remaining allergic reactions were due to other food substances: 6 (11.8%), 4 (7.8%), 12 (23.5%), 11 (21.5%) subjects reacted to wheat, potato, milk, and egg, respectively. The 2 subjects reacting to Sinlac® and Sinlac®AP were both also reacting to egg only. Six infants were given unlisted allergenic food products by their parents; 2 had a positive reaction to banana and to banana and carrot respectively.

Both Sinlac® and Sinlac®AP were significantly better tolerated by atopic infants (ITT population: P<0.0001; PP population: P=0.005) when compared to allergenic foods (WMEP) (Table 2). However, no statistically significant difference was observed between Sinlac® and Sinlac®AP (ITT and PP populations: P=1.00).

	ITT population			PP population		
	N	Allergic reaction		N	Allergic reaction	
		No	Yes	No	Yes	
WMEP	51	51% (26)	49% (25)	25	52% (13)	48% (12)

Sinlac®	51	98% (50)	2% (1)	25	96% (24)	4% (1)
Sinlac®AP	51	98% (50)	2% (1)	25	96% (24)	4% (1)

Table 2: Allergic reactions (ITT and PP populations) (numbers in parentheses are frequencies).

During the study period, 83 AEs were reported. They were unrelated or unlikely to be related to the study products, with the exception of two (croup and rhinitis of mild severity). The risk of AEs was higher in the WMEP group compared with the Sinlac® and Sinlac®AP groups; inter-group differences were however not statistically significant (P=0.08). Differences between the Sinlac® and Sinlac®AP groups were not statistically significant either (P=1.00).

Conclusion

In this exploratory clinical study based on open-label food challenges, Sinlac® and Sinlac®AP were both very well tolerated by atopic infants and children aged 4 to 40 months. Only 2% showed a positive reaction to these products. In comparison, 49% showed an allergic reaction following ingestion of wheat, potato, milk or hen's egg. The low allergenicity of Sinlac® therefore makes it a safe alternative for highly allergic infants having or not multiple food allergies (but excluding infants allergic to rice and/or carob).

If the benefit of AP supplementation in hypoallergenic cereals, i.e. benefit of AP addition, remains to be demonstrated, the results observed with Sinlac® and Sinlac®AP appeared to be similar, thus suggesting that adding AP to the commercial recipe would not have any negative effect on the tolerability of the product.

Acknowledgment

The authors thank Annick Mercenier for scientific input, Laura Gosoniu for expert statistical support, Sonia Frappier for her assistance in the clinical trial set-up, Massimo Fontanesi for the production of the study products SINLAC® and SINLAC® AP, and Christele Closse who provided medical writing services on behalf of Nestle.

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