

Efficacy and Safety of Soy Protein Based Formula in Atopic Dermatitis

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Abstract

Soy protein based formula (SPF) has been developed for infants who are at a high risk for atopic dermatitis (AD) and cow's milk protein allergy (CMA). We performed this study to evaluate the therapeutic efficacy and safety of SPF compared to conventional hydrolyzed cow's milk formula (hCMF) in the feeding of infants with AD and CMA. 38 infants (12 to 24 months of age) diagnosed with CMA and AD were randomized to receive either SPF or hCMF for 12 weeks. Follow-up was conducted at 4, 8 and 12 weeks. Growth parameters of the infants were evaluated during each visit. Clinical evaluations, including AD severity scores, pruritus, specific immunoglobulin E (IgE) (cow's milk protein and soy protein) levels of peripheral blood, were made at enrollment and week 12. Analysis was performed on the 32 infants (SPF: n=16, hCMF: n=16) who completed the 12-week intervention. Eczema area and severity index (EASI) scores, a measure of the severity of AD, and pruritus were significantly reduced after 12 weeks compared to enrollment in the both groups; however, the median changes for EASI scores and pruritus were not statistically different between the two groups. The growth parameters did not differ significantly between both groups at any assessed time point. This study suggests that SPF could be useful in decreasing the severity of AD without affecting infant growth status. Therefore SPF could provide an adequate and safe alternative to hCMF in treating infants with AD and CMA during the first 12 to 24 months of their life.

Key words: atopic dermatitis, cow's milk allergy, hydrolyzed cow's milk formula, soy protein based formula

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing skin disease characterized by itching and skin inflammation. AD commonly manifests during infancy and early childhood and symptoms may improve or disappear during adulthood. An estimated 45% of people with AD develop symptoms within the first 6 months of life and 60~65% develop symptoms within the first year (1-3). AD has been associated with a wide variety of complications, including clinical, behavioral, and financial distress. Specifically, this disease has been associated with infant discomfort, sleep disturbance, irregular feeding, familial stress, increased physician visits, and a financial burden to the family and the healthcare system. Furthermore, AD is considered to be the initial step in atopic march and plays a critical role in the development of allergic rhinitis and/or asthma (4,5). Therefore, preventing and/or alleviating the symptoms of AD have high clinical and social values. The specific etiology of AD is unknown, although a combination of genetic, immunological, and environmental factors likely plays a significant role in the pathogenesis of this disease. Up to 33% of children

with AD have experienced food hypersensitivity to different food allergens, making food allergy a known provoking cause of AD (6). The most common and important food allergen associated with AD is cow's milk protein. About 40~50% of children less than 1 year of age with CMA have AD (7) and a previous study have demonstrated the role of the allergen in inducing and increasing the severity of AD in children (8). Many studies have shown a reduced incidence of AD among infants who were exclusively breast-fed (9). Several formulas, including soy protein based formula (SPF), hydrolyzed cow's milk formula (hCMF) (partially, extensively), and amino acid based formula, have been developed for infants who are not exclusively breast-fed in an effort to reduce the risk of CMA. The allergy-preventing and therapeutic effect of hCMF in infants at a high risk for AD has been demonstrated in many studies (10,11). However, there is no convincing evidence or recommendation for the use of SPF by infants with AD and CMA. We performed this study to evaluate the therapeutic efficacy and safety of SPF compared to conventional hCMF in feeding infants with AD and CMA.

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MATERIALS AND METHODS

From 2008 to 2010, 38 infants (12 to 24 months of age), diagnosed with AD and CMA, were recruited. All infants enrolled in this study met the following inclusion criteria: 1) diagnosis of AD according to criteria of Hanifin and Rajka (12), 2) normal term baby (gestational age ≥ 37 weeks, birth weight ≥ 2.5 kg), and 3) infants who have clinical symptoms of CMA (mainly erythema, and itching related to the consumption of cow's milk) with the presence of serum specific immunoglobulin E (IgE) to cow's milk protein. The exclusion criteria were: 1) preterm baby, 2) infants with a congenital or acquired metabolic disease, and 3) infants with presence of serum specific IgE to soy protein. All participants were provided with mild topical corticosteroids (0.05% desonide lotion) at enrollment and instructed to use it as needed. The infants required no oral medications, including antihistamines, antibiotics, or steroids during the study. Parents of these patients gave written consent, and the institutional review board (IRB) of the Seoul National University Hospital (Seoul, Korea) approved this study.

Study formulas

Following 12 weeks of study, participants were randomized to take either SPF (Premium Vegemel Toddler 2nd step, Dr. Chung's Food Co., Seoul, Korea) or conventional hCMF (Absolute Babywell HA, Maeil Dairies Co., Seoul, Korea). For eligibility, infants were required to take 380 mL/day of each formula. A follow-up was conducted at 4, 8 and 12 weeks. Parents of the study subjects were advised to discontinue the intake of cow's milk and other dairy products throughout the study. Before each visit, the caregivers were required to fill out a 3-day food record to calculate actual amount of intake and caloric intake.

Evaluations

Clinical evaluations, including AD severity scores, pruritus, and specific IgE (cow's milk protein, soy protein) levels of peripheral blood, were made at enrollment and week 12. The pediatric dermatologist, unaware of patients' formula, evaluated AD severity using Eczema Area and Severity Index (EASI) score (13). EASI separately assesses for the key signs of erythema (E), induration (I), excoriations (Ex), and lichenification (L) on a 6-point scale (0~6) on the head/neck, trunk, upper limbs, and lower limbs. Scores: 0=no eruption; 1 $\leq 10\%$; 2 $\leq 10\sim 29\%$; 3 $\leq 30\sim 49\%$; 4 $\leq 50\sim 69\%$; 5 $\leq 70\sim 89\%$; and 6 $\leq 90\sim 100\%$. The average degree of severity of each sign in each of the four body regions was assigned a score of 0 to 3 (none, mild, moderate, and severe, respectively). The total body score for each body

region was obtained by multiplying the sum of the severity scores of the four key signs by the area score, then multiplying the result by the constant weighted value assigned to that body region. The final score is calculated by using the following equation:

$$\text{Head/neck (H)} = (E + I + \text{Ex} + L) \times \text{area} \times 0.2$$

$$\text{Upper limbs (UL)} = (E + I + \text{Ex} + L) \times \text{area} \times 0.2$$

$$\text{Trunk (T)} = (E + I + \text{Ex} + L) \times \text{area} \times 0.3$$

$$\text{Lower limbs (LL)} = (E + I + \text{Ex} + L) \times \text{area} \times 0.3$$

$$\text{EASI} = \text{sum of the above 4 body region scores}$$

Patients' caregivers also reported the pruritus in the form of a visual analogue scale (VAS) from 0 (no itching) to 10 (worst). Serum samples from infants were collected at the time of the initial and final visit. The samples were analyzed for antigen-specific IgE (milk, soy) antibodies using the Pharmacia ImmunoCap System (Pharmacia Diagnostics, Uppsala, Sweden). Growth parameters including height, weight, and head and chest circumferences were evaluated at each visit.

Statistical analysis

Student's *t*-test was used for the comparative study of quantitative variables such as height, weight, and head circumference. Mann-Whitney U-test was performed for any quantitative variables that did not follow normal distribution between the groups. All analyses were conducted by the SPSS statistics program (SPSS version 12.0, SPSS Inc., Chicago, IL, USA). A *p*-value < 0.05 was considered statistically significant.

RESULTS

38 infants diagnosed with AD and CMA were enrolled. 6 (15.8%) dropped out during the study. In hCMF group, 5 of the 21 infants dropped out because of noncompliance (unacceptable taste of the formula). 1 of the 17 infants in the SPF group dropped out because of a follow-up violation. Final analysis was performed on 32 infants (SPF: $n=16$, hCMF: $n=16$) who completed the 12-week intervention. The distribution of characteristics regarding age, sex, and severity of AD, shown in Table 1, were not significantly different between the two groups. Actual amounts of formula were calculated as a daily intake ratio of formula per 380 mL/day and there was no significant difference between the two groups (SPF: $98.21 \pm 31.7\%$ hCMF: $94.78 \pm 29.0\%$, $p > 0.05$, Fig. 1).

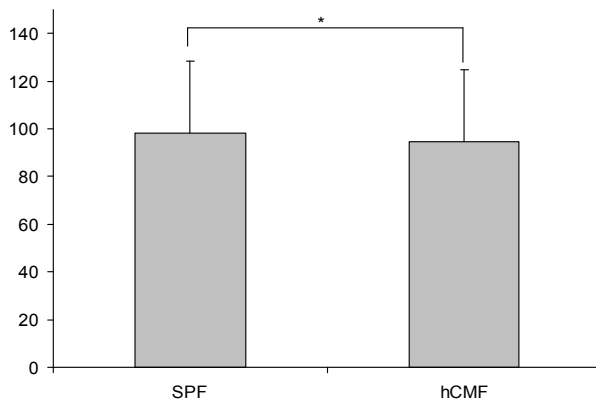
Clinical evaluations of AD

EASI scores and pruritus were significantly reduced at week 12 compared to enrollment in the both SPF and hCMF groups ($p < 0.05$), but the EASI scores median change was not statistically different between the two

Table 1. Baseline characteristics of the study population

	SPF (n=16)	hCMF (n=16)	Total (n=32)	p-value
Gender (male:female)	10:6	9:7	19:13	NS
Age in months	16 (12~23)	15 (12~23)	15.5	NS
Initial EASI score	3.6 (0.8~7.2)	3.8 (0.5~8.7)	3.7	NS

SPF: soy protein based formula, hCMF: hydrolyzed cow's milk formula. Data presented as mean value. NS: non-significant ($p>0.05$). EASI: Eczema Area and Severity Index.

**Fig. 1.** Dietary intake ratio of formula for 12 weeks. SPF: soy protein based formula. hCMF: hydrolyzed cow's milk formula. * $p>0.05$.

groups (Δ EASI score: SPF/hCMF: -2.8/-0.9, $p=0.076$, Table 2). Also, the median change of pruritus was not statistically different between the two groups (Δ VAS of pruritus: SPF/hCMF: -2.5/-2.0, $p=0.954$, Table 2).

The level of serum-specific IgE (milk and soy) was measured to evaluate the allergy status of infants at enrollment and the end of the study. The mean concentration of serum-specific milk IgE in hCMF group was 2.12 (0.8~4.18) IU/mL (pre-treatment) and 2.03 (0.74~4.01) IU/mL (post-treatment) compared to 2.49 (1.43~3.65) IU/mL (pre-treatment) and 2.00 (1.83~3.63) IU/mL (post-treatment) in the SPF group. No significant difference was observed in the level of specific milk IgE between hCMF and SPF groups at both pre- and post-treatment times ($p=0.522$). For all the infants enrolled in the study, concentrations of serum-specific soy IgE measured at baseline were all under detectable or at low levels (<0.69 IU/mL). After treatment, each group revealed no significant difference in the level of specific

Table 2. EASI score and VAS of pruritus

		0 week	12 week	Δ
EASI	SPF	4.1 ^a	1.3 ^b	-2.8*
	hCMF	2.0 ^a	1.1 ^b	-0.9*
Pruritus	SPF	5.0 ^a	2.5 ^b	-2.5**
	hCMF	5.0 ^a	3.0 ^b	-2.0**

SPF: soy protein based formula, hCMF: hydrolyzed cow's milk formula. Data presented as median. EASI: Eczema Area and Severity Index.

^{ab} $p<0.05$, * $p=0.076$, ** $p=0.954$.

soy IgE ($p=0.821$).

Growth status evaluations

To evaluate the effect on growth of SPF feeding infants, we compared growth parameters of all patients at each visit. No differences were observed between conventional hCMF and SPF groups regarding their height, weight, and head and chest circumferences (all $p>0.05$, Fig. 2). Final growth data measured at week 12 showed no differences between both groups and all were in the normal range (Table 3).

DISCUSSION

Soy protein-based formula (SPF) was first described as a cow's milk substitute in 1909, but was not used for feeding babies with cow's milk allergy (CMA) until 1929. Since then, SPFs have been widely used for feeding babies with CMA. Despite limited indications, SPF accounts for approximately 20% of the formula market in the United States (14). The distribution of nutrients in SPFs is quite similar to cow's milk formulas, as both contain the same amount of proteins, lipids derived from vegetables oils, and carbohydrates in the form of maltodextrins, cornstarch, or sucrose. All SPFs are lactose free, fortified with L-methionine, and contain added taurine, carnitine, and iron (14,15). According to demonstrations in clinical studies and literature reviews, infants fed SPFs showed nutritional adequacy, normal growth, sexual development, immune function and neurodevelopment equivalent to those achieved with cow's milk formulas. The US Food and Drug Administration has approved SPFs as safe for use with infants (16). However, recent publications have recommended that SPFs should not be used during the first 6 months of life for infants with a food allergy (17). Therefore, these

Table 3. Growth parameters at week 12

	SPF	hCMF	p-value
Height (cm)	82.7 \pm 4.8	82.8 \pm 3.5	NS
Weight (kg)	11.4 \pm 1.8	11.1 \pm 1.4	NS
Head circumference (cm)	48.1 \pm 1.8	47.2 \pm 1.4	NS
Chest circumference (cm)	51.0 \pm 2.9	49.5 \pm 2.2	NS

SPF: soy protein based formula, hCMF: Hydrolyzed cow's milk formula. Data presented as mean \pm SD (standard deviation). NS: non-significant ($p>0.05$).

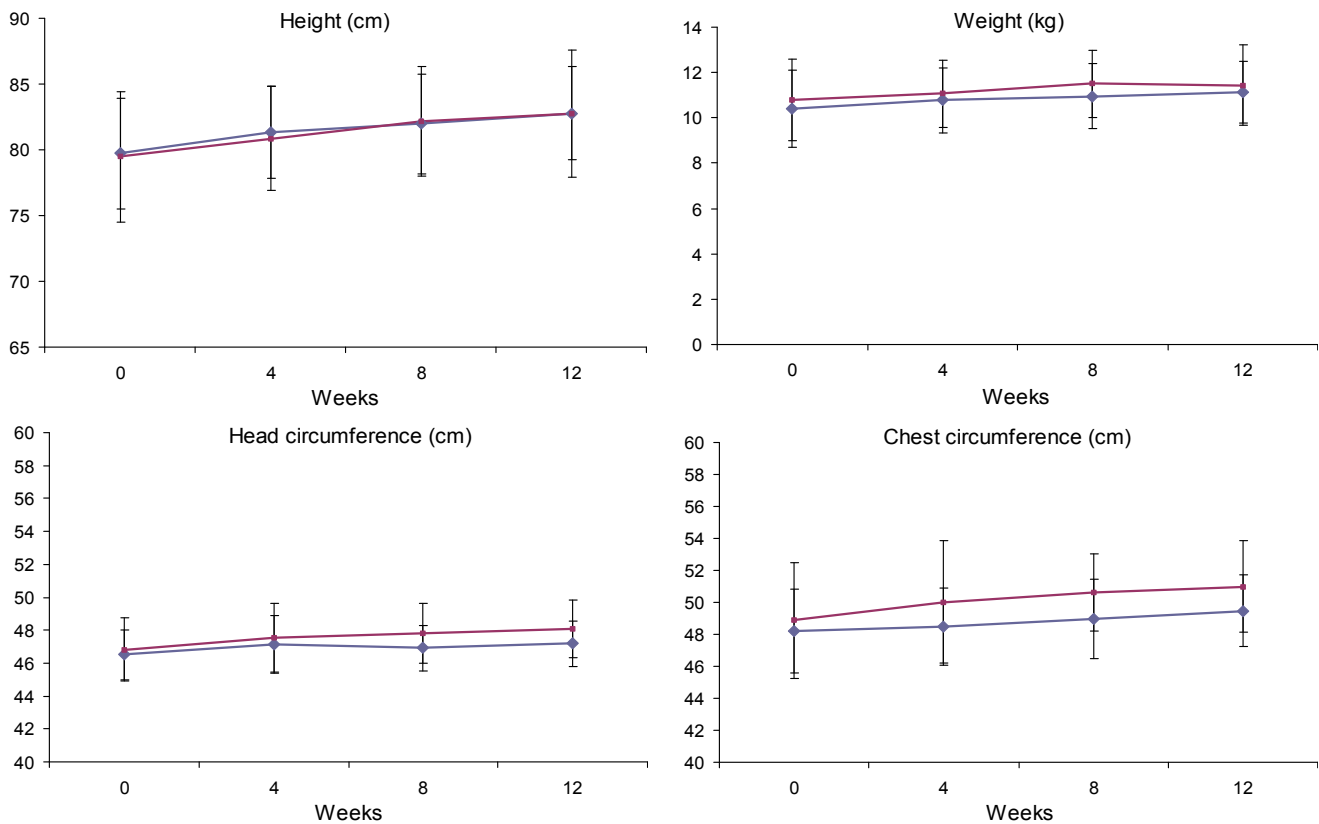


Fig. 2. Growth parameters. ■ soy protein based formula, ◆ hydrolyzed cow's milk formula.

recommendations limit the use of SPF. With the current SPFs, bone mineralization, serum concentrations of calcium and phosphorus, and alkaline phosphatase concentrations in term infants through 12 months of age are equal to those seen in infants fed cow's milk formulas (18). According to several recommendations, our study was limited to infants 12 to 24 months of age.

The allergy-preventing and therapeutic effect of hCMF in infants at a high risk for AD has been demonstrated in several studies (10,11). However, no convincing evidence or recommendation is available for the use of SPF in infants with AD and CMA. Cantani et al. (19) administered SPFs, as a cow's milk substitute, to 21 infants with AD due to cow's milk hypersensitivity. All infants developed regularly and, most importantly, skin lesions had improved.

We conducted the first randomized double-blind controlled study evaluating the therapeutic effect and safety of SPF on infants with AD and CMA. When compared to conventional hCMF, SPF showed similar clinical improvements and growth status. This result suggests that SPF can be used as another maintenance treatment for infants with AD and CMA.

One rationale for using SPF is the assumption that soy protein is less antigenic than cow's milk protein (20). Hydrolyzed formulas may contain small amounts of na-

tive proteins from which the product is derived, whereas no intact cow's milk protein is present in SPFs. According to experimental and clinical studies, soy proteins are less immunogenic and allergenic than cow's milk proteins. Unlike hydrolyzed formulas, SPFs do not cross-react with cow's milk proteins (21).

However, this rationale has been questioned because soy protein may also cause an allergic disease, as some infants with CMA are also allergic to soy protein (22,23).

Since sensitization to soy has been reported in 10~14% of infants with CMA, the introduction of SPF should be careful. In this study, a possible secondary sensitization to soy was not found in either the SPF or hCMF groups.

This study has several limitations. First, the severity of recruited AD patients was mild in both groups (low initial EASI score). Thus, we could not evaluate the effect of SPF on moderate to severe AD patients who require a more active treatment. Other limitations included a small sample size and possible confounders such as seasonal changes in temperature and humidity or environmental exposure to allergens and pollution. Lastly, we did not assess food allergens other than cow's milk protein and soy protein.

In conclusion, SPF is an effective and well-tolerable treatment option for infants with AD and CMA. Therefore,

SPF provides an adequate and safe alternative to hCMF in treating infants with AD with CMA during the first 12 to 24 months of their life. However, the underlying mechanism and effect of SPF on the immune system should be further evaluated.

ABBREVIATIONS

AD, atopic dermatitis; CMA, cow's milk allergy; hCMF, hydrolyzed cow's milk formula; SPF, soy protein based formula.

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