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Original Article

The influence of breastfeeding in breast-fed infants with atopic dermatitis

Hao-Pai Lin [a], Bor-Luen Chiang [b], Hsin-Hui Yu [a], Jyh-Hong Lee [a], Yu-Tsan Lin [a], Yao-Hsu Yang [a], Li-Chieh Wang [a,*]

[a] Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan
[b] Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan

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Abstract *Background:* The aim of this study was to evaluate whether breastfeeding should be discontinued for exclusively breast-fed infants with atopic dermatitis (AD).
Methods: Eighty-seven exclusively breast-fed infants with AD were enrolled in a prospective observational study. The infants were divided into 3 groups: breastfeeding only (BM group), partial breastfeeding and partial partially hydrolyzed whey formula (pHF-W) (Partial group) and pHF-W only (DC group). The extent and severity of AD were evaluated with the Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) index at enrollment and 3 and 6 months later.
Results: There were no significant differences in parental atopy history, PO-SCORAD scores, and medication scores at baseline. At month 3 and 6, the PO-SCORAD scores were significantly decreased in all groups. PO-SCORAD scores at month 3 and 6 and at the last time point when topical corticosteroids were given were significantly different among the groups. Stepwise multiple linear regression analysis showed that baseline PO-SCORAD scores and stopping breastfeeding were significantly associated with month 3 PO-SCORAD scores ($p < 0.001$), after adjusting for sex, age, baseline medication scores, partial breastfeeding and parental atopy history. In addition to baseline PO-SCORAD scores and stopping breastfeeding, partial breastfeeding was significantly associated with month 6 PO-SCORAD scores. Long-term follow-up showed that only stopping breastfeeding was significantly associated with the last time point when topical corticosteroids were given ($p = 0.014$).
Conclusion: For exclusively breast-fed infants with AD, discontinuing breastfeeding and shifting to pHF-W might help to improve symptoms and shorten the duration of AD regardless of sex, age and parental atopy history.

* Corresponding author. Department of Pediatrics, National Taiwan University Hospital, 7 Chung Shan South Road, Taipei 100, Taiwan. Fax: +886 2 2311 9087.
E-mail address: lindawang@ntu.edu.tw (L.-C. Wang).

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Introduction

The impact of breastfeeding on the development of atopic diseases such as atopic dermatitis (AD), asthma, or allergic rhinitis has been thoroughly investigated. Although the protective effect of breastfeeding against development of AD[1–3] and cow's milk allergy during childhood is well accepted,[1] the subject remains controversial.[4–10] A prospective study in Japan showed that both exclusive breastfeeding for more than 4 months and partial breastfeeding for more than 6 months were associated with an increased risk of AD among infants with no parental history of allergic disorders.[5] Two cohort studies in Taiwan also showed that prolonged breastfeeding increased the risk of AD in children at 18 months of age.[7] A meta-analysis of prospective cohort studies performed in 2008 found insufficient evidence that exclusive breastfeeding for at least 3 months is protective against AD, even in children with a positive family history of atopy.[11] These conflicting results are likely due to confounding effects from differences in genetic background, health literacy, socioeconomic status, and other maternal health behaviors.

Since the preventative role of breastfeeding in the development of AD is in doubt, should we encourage breastfeeding in infants with AD? To date, there is no consensus on breastfeeding for infants with progressive AD during the period of exclusive breastfeeding, even if they are receiving standard treatment for AD such as topical corticosteroids and emollients. As early as 1999, an observational study of 100 infants suggested that symptoms of AD significantly improved after cessation of breastfeeding.[12] However, this study lacked a control group, so the results couldn't confirm whether the improvement in symptoms was due to cessation of breastfeeding or to the natural course of the disease.

Therefore, we designed a study to clarify whether breast-fed infants with AD should continue exclusive breastfeeding. To determine this, we evaluated the difference in severity of AD at three time points, enrollment and 3 and 6 months after study entry, among infants who remained on breastfeeding, those who were switched to a partially hydrolyzed whey formula (pHF-W) partially and those who discontinued breastfeeding and received pHF-W only.

Methods

Infants with physician-diagnosed AD being exclusively breast-fed were enrolled in a study at the National Taiwan University Hospital (NTUH) from February 2009 to September 2012. The diagnosis of AD was based on the criteria established by Hanifin and Rajka, and included the following major features: a family history of AD, the presence of pruritus, typical morphology and distribution of lesions, and chronic or relapsing skin lesions.[13,14] Infants with major diseases such as cardiovascular anomalies, pulmonary dysfunction, or neurological deficits, for example, were excluded from the study. The study was approved by the Ethics Committee of NTUH and informed consent was obtained from all participants and their guardians. All the basic characteristics such as sex, age, parental atopy history, onset age of AD, and maternal intake of probiotics during breast feeding period were obtained at enrollment. The atopy history included ever asthma, allergic rhinitis and/or atopic dermatitis in baby's mother or father. Parental atopy history was positive when atopy history was noted in either one or two parents.

Exclusive breastfeeding was defined when the infant was being given only breast milk, without the addition of infant formula and/or cow's milk. Patients were divided into 3 groups according to their milk intake on parent's will: (1) infants exclusively fed by breastfeeding (BM group); (2) infants receiving partial breastfeeding and partial pHF-W (Partial group); and (3) infants no longer being breastfed and exclusively receiving pHF-W (DC group). Infants in the Partial and DC groups received the same pHF-W (NAN H.A.® 1 or 2, Nestlé Ltd., Frankfurt, Germany). Solid food was introduced beginning at 6 months of age in all groups, except in few patients who were enrolled after they were 6 months of age. These infants had been started on solid food since enrollment. All parents were asked to delay introducing allergenic foods such as egg white and shellfish until their child was 10—12 months of age.

The severity of atopic dermatitis was assessed with the Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) index,[15] a self-assessment score that allows parents to comprehensively evaluate the actual course of AD. The extent and severity of AD evaluated by PO-SCORAD scores were obtained at enrollment and 3 and 6 months later. Standard treatments for AD, including topical corticosteroids, antihistamines, topical antibiotics, emollients, and even systemic corticosteroids, were prescribed with titration during the study period. The dosage of systemic corticosteroids (oral prednisolone) is 1 mg/kg/day for 3 days in severe patients. All the medications were reviewed from the patient's medical chart. The medication score was defined as the monthly prescribed topical corticosteroids (tubes; fluticasone propionate, 5 g/tube) plus 5 times oral corticosteroids (bottles; prednisolone sodium [phosphate], 1 mg/mL, 60 mL/bottle).

Statistical analysis

We compared the sex, parental atopy history, and maternal intake of probiotics among the 3 groups using the Pearson's Chi square test. We compared the PO-SCORAD scores at baseline, month 3 and 6, the medication scores, and the mean ages among the 3 groups using the Kruskal—Wallis test. The changes in PO-SCORAD scores between different time points, representing improvement in severity of symptoms, were compared using the Wilcoxon signed-rank test. Stepwise multiple linear regression analysis was used to determine whether the outcomes (PO-SCORAD scores at month 3 and 6, and the last time point when topical corticosteroids were given) were associated with feeding type, after adjusting for factors including age, sex, baseline medication scores, baseline PO-SCORAD scores, and parental atopy history. The differences of proportion of patients using topical corticosteroids were analyzed by the Kaplan—Meier method using a log-rank test. A p value < 0.05 was considered significant. A p value < 0.1 and ≥ 0.05 was considered as a trend. All statistical analyses

were performed with IBM SPSS statistical software (version 20.0.0, IBM Corp., Armonk, NY).

Results

The method of data collection used in this study is shown in Fig. 1. Eighty-seven infantile AD patients with exclusive breastfeeding were enrolled for the first interview. Only 66 infants were brought in for the month 3 interview, and 50 infants completed the study. The other 21 infants were lost to follow-up when their parents refused phone contact and/or were unable to report PO-SCORAD data. At the month 3 interview, there were 23 subjects in the BM group, 12 in the Partial group and 31 in the DC group (Fig. 1). Although only three-fourths of the infants completed the study at month 6, we were able to obtain data on long-term medications from medical charts for more than 90% of the infants.

A comparison of the baseline characteristics among the three groups is shown in Table 1. The mean age at enrollment (shown as mean ± standard error) was 5.57 ± 0.30, 4.75 ± 0.33, and 5.90 ± 0.25 months in the BM, Partial and DC groups, respectively ($p = 0.045$). The percentages of male infants in the BM, Partial and DC groups were 65.2%, 33.3%, and 83.9%, respectively ($p = 0.006$). There were no significant differences in age at disease onset, parental history of atopy, or maternal intake of probiotics among the groups. The baseline PO-SCORAD scores in the BM, Partial and DC groups were 23.91 ± 2.59, 30.08 ± 3.75, and 27.58 ± 1.92, respectively. These scores were not significantly different among groups (Table 2). At month 3, the PO-SCORAD scores were significantly different among the 3 groups ($p = 0.035$); however, at month 6, the PO-SCORAD scores were not significantly different. The symptoms of AD improved with time in all groups, with significantly decreases in PO-SCORAD scores. The decreases of the PO-

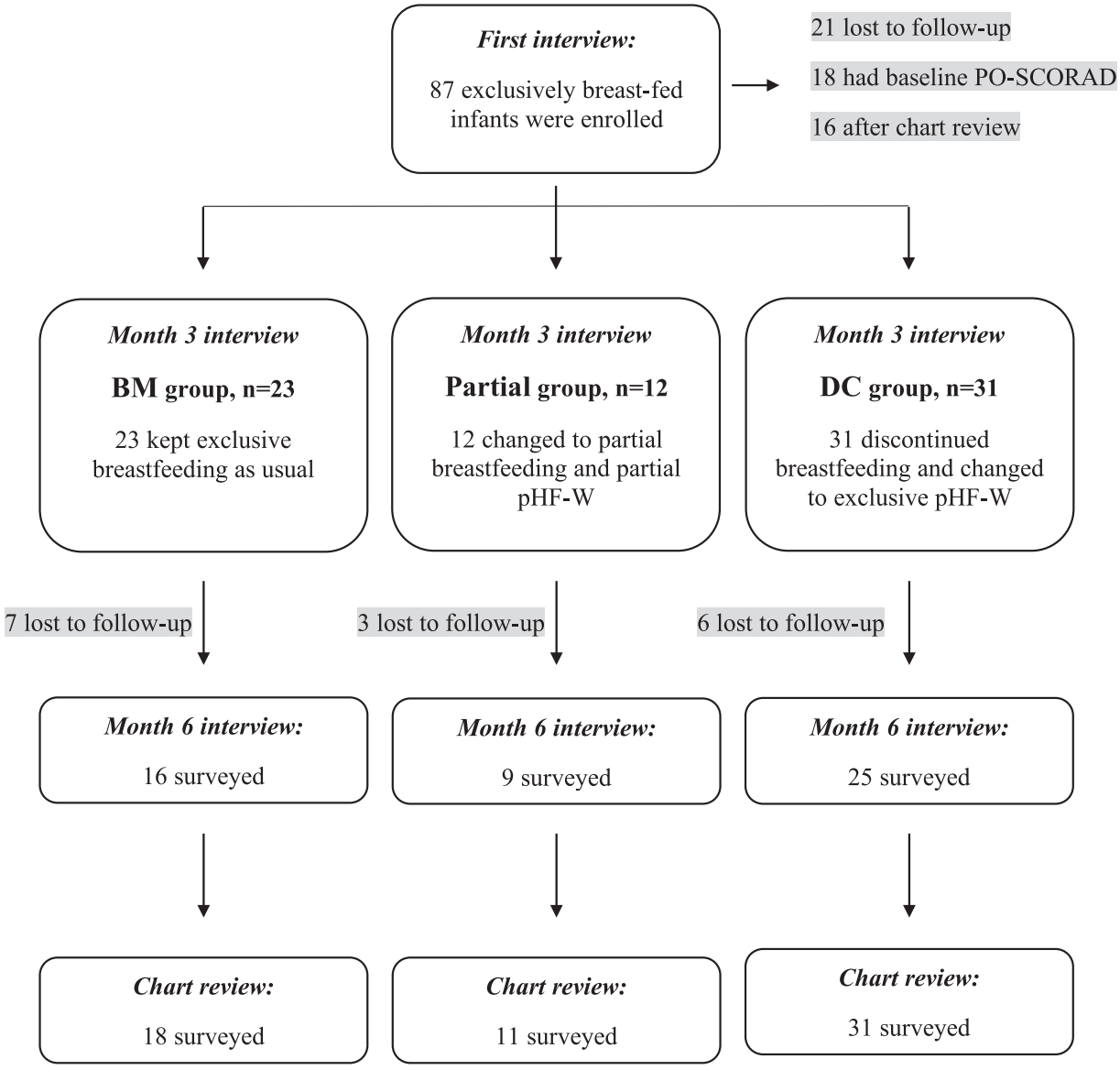

Figure 1. A flow chart showing the method of data collection.

Table 1 A comparison of the baseline characteristics among 3 groups with infantile AD.

Characteristics	BM group (n = 23)	Partial group (n = 12)	DC group (n = 31)	*p* value[a]
Sex (n, %)				
Male	15 (65.2%)	4 (33.3%)	26 (83.9%)	**0.006**
Female	8 (34.8%)	8 (66.7%)	5 (16.1%)	
Age at enrollment (months)				
Mean ± SE (Interquartile range)	5.57 ± 0.30 (4–6)	4.75 ± 0.33 (4–6)	5.90 ± 0.25 (5–7)	**0.045**
Age at onset (months)				
Mean ± SE (Interquartile range)	2.83 ± 0.3 (2–3.5)	1.71 ± 0.2 (1–2.38)	2.08 ± 0.22 (1–3)	0.063
Paternal atopy history (n, %)	12 (52.2%)	9 (75%)	19 (61.3%)	0.421
Maternal atopy history (n, %)	11 (47.8%)	9 (75%)	14 (45.2%)	0.194
Parental atopy history (n, %)	15 (65.2%)	11 (91.7%)	24 (77.4%)	0.213
Maternal intake of probiotics (n, %)	2 (8.7%)	2 (16.7%)	3 (9.7%)	0.748

Bold values denotes significant *p* values (<0.05).
[a] Using the Pearson's Chi square test or the Kruskal–Wallis test to compare differences among the three groups.

Table 2 The PO-SCORAD rating among 3 groups with infantile AD at baseline, month 3 and 6.

	BM group	Partial group	DC group	*p* value[b]
Baseline PO-SCORAD				
Mean ± SE (Interquartile range)	23.91 ± 2.59 (17–30)	30.08 ± 3.75 (19–41.5)	27.58 ± 1.92 (20–32)	0.181
Month 3 PO-SCORAD				
Mean ± SE (Interquartile range)	16.26 ± 2.04 (8–24)	17.83 ± 3.31 (7–30)	10.26 ± 1.58 (5–14)	**0.035**
Month 6 PO-SCORAD				
Mean ± SE (Interquartile range)	11.69 ± 3.08 (0–23)	9.44 ± 2.14 (3.5–15)	5.08 ± 1.22 (0–7.5)	0.109
Month 3 − baseline PO-SCORAD difference				
Mean ± SE (Interquartile range)	−7.65 ± 1.19 (−11 to −4)	−12.25 ± 1.74 (−16.5 to −8.25)	−17.32 ± 1.62 (−22 to −12)	**<0.001**
p value[a]	**<0.001**	**0.002**	**<0.001**	
Month 6 − baseline PO-SCORAD difference				
Mean ± SE (Interquartile range)	15.00 ± 2.13 (−19.75 to −8)	−23.44 ± 3.33 (−30 to −18)	−22.72 ± 1.83 (−25 to −16)	**0.028**
p value[a]	**<0.001**	**0.008**	**<0.001**	
Month 6 − month 3 PO-SCORAD difference				
Mean ± SE (Interquartile range)	−7.31 ± 1.74 (−12 to −2)	−10.33 ± 2.44 (−16.5 to −2)	−5.96 ± 1.10 (−8.5 to 0)	0.330
p value[a]	**0.001**	**0.018**	**<0.001**	

Bold values denotes significant *p* values (<0.05)
[a] Using the Wilcoxon signed-rank test to compare the PO-SCORAD values in different time points within group.
[b] Using the Kruskal–Wallis test to compare differences among the three groups.

SCORAD scores among groups were significantly different from baseline to month 3 and baseline to month 6 ($p < 0.001$, $p = 0.028$, respectively) (Table 2 and Fig. 2).

The medication scores at baseline and during the study period were not different among the 3 groups (Table 3). At the chart review, the last topical corticosteroids age, or the last time point when topical corticosteroids were given, were significantly different among the 3 groups ($p = 0.008$). The last topical corticosteroids age in the BM, Partial, and DC groups was 36.21 ± 5.96, 20.50 ± 6.31, and 16.03 ± 2.95 months, respectively. The number of patients using topical corticosteroids decreased with age (Fig. 3). Before 8 months of age, fewer patients in the DC group were receiving topical corticosteroids treatment than was true of the other 2 groups; after 8 months of age, the use was almost the same among the Partial and DC groups. At the end of follow-up, no patients in the DC and Partial groups were using topical corticosteroids; in contrast, 23.5% patients in the BM group were still being treated with topical corticosteroids. The curves for the proportion of patients using topical corticosteroids were significantly different among the 3 groups ($p = 0.018$).

We used stepwise multiple linear regression analysis to detect the influence of breastfeeding on the severity of AD. The results showed that baseline PO-SCORAD scores (regression coefficient: 0.615; $p < 0.001$), and complete cessation of breastfeeding (regression coefficient: −7.710; $p < 0.001$) were significantly associated with the PO-SCORAD scores at month 3, after adjusting for sex, age, baseline medication scores, partial breastfeeding status, and parental atopy history (Table 4). Baseline PO-SCORAD scores (regression coefficient: 0.471; $p < 0.001$), complete cessation of breastfeeding (regression coefficient: −7.809; $p = 0.001$), and partial breastfeeding (regression coefficient: −6.533; $p = 0.032$) were all significantly associated with the PO-SCORAD scores at month 6. When

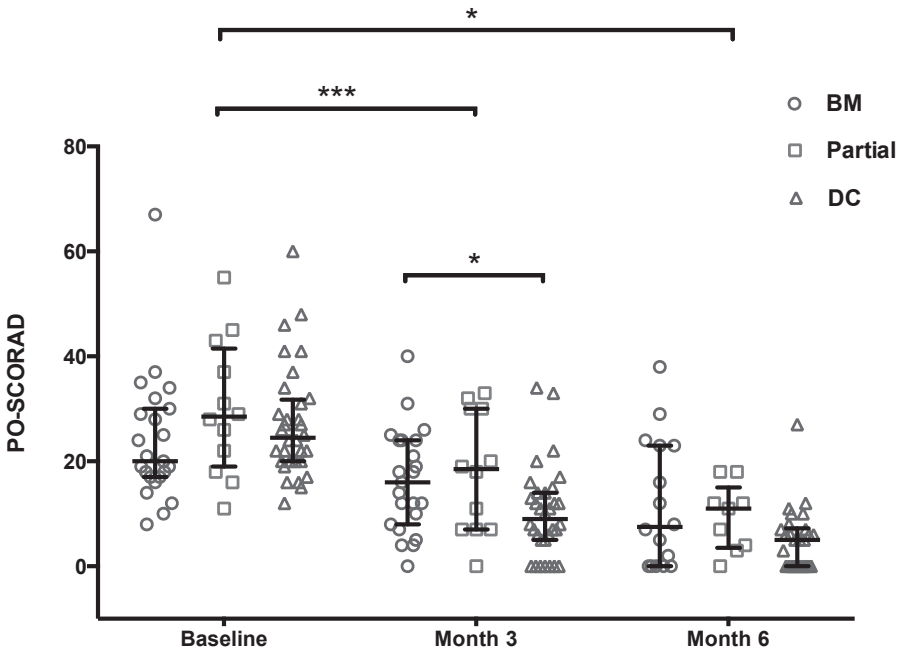

Figure 2. The severity of AD at different time points. The PO-SCORAD of the BM group (circles), Partial group (squares) and DC group (triangles) are shown at baseline, month 3 and 6. The intersecting lines represent the median with interquartile range (*, $p < 0.05$; ***, $p < 0.001$).

Table 3 A comparison of the medication scores among 3 groups with infantile AD.

	BM group (n = 16)	Partial group (n = 11)	DC group (n = 31)	*p* value[b]
Baseline topical corticosteroids usage (tubes)				
Mean ± SE (Interquartile range)	3.25 ± 0.42 (2—4)	2.82 ± 0.44 (2—4)	2.68 ± 0.51 (1—3)	0.139
Baseline medication score[a]				
Mean ± SE (Interquartile range)	3.56 ± 0.63 (2—4)	4.18 ± 1.25 (2—4)	3.32 ± 0.58 (1—4)	0.434
Month 0—6 average medication score				
Mean ± SE (Interquartile range)	1.96 ± 0.61 (0.5—1.95)	1.29 ± 0.47 (0.67—1.33)	1.12 ± 0.19 (0.33—1.83)	0.547
Last topical corticosteroids age (months)				
Mean ± SE (Interquartile range)	36.21 ± 5.96 (13.25—60.5)	20.50 ± 6.31 (7—25)	16.03 ± 2.95 (4.5—25.5)	**0.008**
Follow-up age (months)				
Mean ± SE (Interquartile range)	43.92 ± 5.36 (24.25—62.25)	39.82 ± 8.92 (18.5—64)	41.24 ± 4.64 (14—64.5)	0.747

Bold values denotes significant *p* values (<0.05).
[a] The medication score was defined as the monthly prescribed topical corticosteroids (tubes) plus 5 times oral corticosteroids (bottles).
[b] Using the Kruskal—Wallis test to compare differences among the three groups.

we focused on the long-term effect, we found that complete cessation of breastfeeding (regression coefficient: −13.671; $p = 0.014$) was significantly associated with the last topical corticosteroids age, while partial breastfeeding showed a trend toward this (regression coefficient: −0.285; $p = 0.053$). Thus, complete cessation of breastfeeding had the most significant effect on the improvement of AD.

The cases of 21 infants were lost to follow-up; 18 infants had baseline PO-SCORAD scores but no PO-SCORAD scores at month 3 and 6; and data on the feeding method were missing. Sixteen infants visited the clinic at NTUH continuously. Analysis showed the following basic characteristics: 15 of the 18 infants (83.3%) were male; the mean age at enrollment was 5.21 ± 0.43 months (4—6 months; interquartile range); and the age at onset of AD was 2.64 ± 0.27 (2—3.25) months. Twelve infants (66.7%) had a history of paternal atopy; 7 (38.9%) had a history of maternal atopy; 13 (72.2%) had a history of parental atopy; and none had a history of maternal intake of probiotics.

The baseline PO-SCORAD score was 20.5 ± 1.56 (15—25.75), which was not significantly different among the study subjects. The baseline medication score, 4.81 ± 1.12 (1.5—6.75), and the follow-up age, 42.60 ± 8.02 (11.75—71.25) months, were not significantly different,

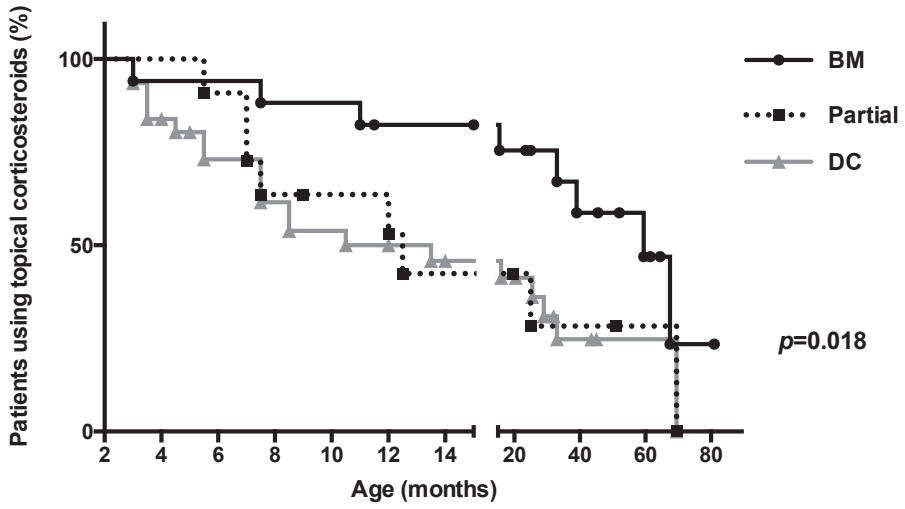

Figure 3. Kaplan–Meier curve for the proportion of patients using topical corticosteroids. The difference among curves is analyzed by a log-rank test.

Table 4 The stepwise multiple linear regression analysis data about the influence on the severity of AD.

	Month 3 PO-SCORAD		Month 6 PO-SCORAD		Last topical corticosteroids age	
	Parameter estimate	*p* value	Parameter estimate	*p* value	Parameter estimate	*p* value
Constant	1.015	0.687	−0.216	0.945	29.704	<0.001
Sex	0.029	0.742	−0.053	0.647	0.023	0.866
Age	−0.019	0.822	−0.047	0.693	−0.126	0.338
Baseline PO-SCORAD	0.615	**<0.001**	0.471	**<0.001**	0.146	0.253
Baseline medication score	0.084	0.327	0.113	0.305	0.026	0.841
DC breastfeeding	−7.710	**<0.001**	−7.809	**0.001**	−13.671	**0.014**
Partial breastfeeding	−0.095	0.329	−6.533	**0.032**	−0.285	0.053
Parental atopy history	−0.033	0.693	0.018	0.872	0.052	0.684

Bold values denotes significant *p* values (<0.05).

either. The last topical corticosteroids age was 34.56 ± 8.27 (7.25–54) months, which was similar to that of the BM group and was significantly different when we compared the 4 groups (the BM, Partial, DC, and loss to follow-up groups; $p = 0.011$).

Discussion

This study investigated the effects of breastfeeding on infants with AD. In this study, we used physician-diagnosed AD instead of questionnaire data based on the presence of an itchy rash in previous study,[16] which may therefore include non-atopic eczema, such as seborrheic or contact dermatitis. For the breast-fed infants with AD, complete cessation of breastfeeding and a shift to pHF-W may improve AD symptoms under standard treatment with less PO-SCORAD values at month 6 and younger age free of topical corticosteroids. Since the medication score was not significantly different among the 3 groups at baseline and during the study period, the consideration of treatment effect on PO-SCORAD scores could be overlooked. Although the regression analysis shows the significant effect of baseline PO-SCORAD scores on PO-SCORAD scores at month 3 and 6, as more severe disease at the initial interview remained more severe at month 3 and 6, the effect on the long-term outcome of the last topical corticosteroids age was not significant. The long-term outcome is associated with cessation of breastfeeding and a trend association in partial breastfeeding. Thus, we recommended that parents of breast-fed infantile AD patients stop or at least decrease their infants' amount of breastfeeding, and shift to feeding with pHF-W.

The European Academy of Allergology and Clinical Immunology reviewed prospective observational studies and concluded that breastfeeding for at least 4–6 months is associated with a decreased risk of cow's milk protein allergy until 18 months of age, and with the risk of AD up to 3 years of age.[17] Interestingly, a more recent systematic review from 2009 did not find strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against AD, even among children at high risk of atopy.[11] In a population-based birth cohort study in Japan (n = 38,757), the authors found that breastfeeding is associated with an increased risk of AD until up to 42 months of age.[18] And, results of a previously mentioned observational study in 1999 suggested that AD symptoms significantly improved after cessation of breastfeeding.[12] Therefore, our data confirmed that breastfeeding may not be beneficial in these infants.

The reason that the cessation of or partial breastfeeding improves AD symptoms by decreasing PO-SCORAD scores at month 3 and 6 and also shortens the disease course may be due to the removal of causative factors. Although breast milk protein is less immunogenic than cow's milk protein, there is still little non-human protein, such as lactoglobulin, in breast milk. Nevertheless, some food allergens have been identified in breast milk. Peanut allergens are rapidly transferred in human breast milk, in some cases as soon as 10 min after peanut ingestion.[19] Although these small amounts of immunogenic allergens were believed to prevent food allergy by oral tolerance, they are still pathogenic in infantile AD. In some infants allergic to cow's milk protein who were exclusively breast-fed, the mothers were advised to stop any milk products intake to attenuate their infants' symptoms.[20] The predominant offending foods were egg, milk, peanuts, soybeans, fish, chocolate, yogurt, soy sauce, and miso soup. Long-term maternal exclusion of these trigger foods led to progressive improvement of skin lesions in the majority of the infants.[21,22] Therefore, food allergens in breast milk might be the cause.

Study results have also shown that the increased risk of AD from breastfeeding progressively increases with the length of time the child has been exclusively breast-fed.[6,7,9] This observation suggests that a risk factor for AD is transmitted via the mother's milk. This may include cytokines, immune cells, antibodies, or polyunsaturated fatty acids.[9,23,24] It has also been documented that several cytokines modulate allergic inflammation in AD.[25] However, previous studies have also reported discordant results with regards to the relationship between cytokines in breast milk and the occurrence of allergic disorders in mothers and their children.[26] A cohort study in Japan reported significant differences in the concentrations of interleukin (IL)-1β and IL-12 p40 in the colostrum, and in those of IL-4, eotaxin, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, interferon (IFN)-α_2, and macrophage inflammatory protein-1α in breast milk between the milk received by infants who developed AD at the age of 6 months and that received by the control infants.[27]

We also collected the breast milk at enrollment and breast milk from healthy infants' mothers. The supernatant of breast milk was assayed by enzyme-linked immunosorbent assay (ELISA) testing. There were no differences between breast milk from infantile AD mothers and that from control mothers in transforming growth factor (TGF)- β, IL-2, IL-5, IL-10 and IFN-γ. However, decoy receptor 3 (DcR3) was significantly higher in breast milk from healthy controls' mothers than that from AD infants' mothers ($p < 0.001$) (Fig. S1). DcR3 is a member of the tumor necrosis factor (TNF) receptor superfamily that competes with Fas ligand (FasL), TNF superfamily-14 (LIGHT), and TNF-like molecule 1A (TL1A).[28] DcR3 is a novel immunosuppressant whose biological functions result in part from its ability to neutralize the activities of TL1A, LIGHT, and FasL, as well as from non-decoy functions. It is likely that soluble DcR3 in breast milk plays a role in the protection against AD.

Although results of the German Infant Nutritional Intervention (GINI) study showed the preventive effect of both partially hydrolyzed formula and extensively hydrolyzed formula in the development of AD, it has been reported that partially hydrolyzed formula may be more beneficial than extensively hydrolyzed formula when development of tolerance is considered. Also, use of the pHF-W is more cost-saving. Therefore, we recommend to mothers that they stop breastfeeding or make a partial shift of breastfeeding to feeding their infants with pHF-W. The beneficial effect on AD of cessation or partial cessation of breastfeeding may not only be a result of removing causative factors. Introducing pHF-W may accelerate development of tolerance. Oral tolerance is the active inhibition of cellular and humoral immune responses to food antigens. Such inhibition occurs through several mechanisms, including the production of regulatory T cells and the deletion of antigen-specific T cells, and the process of dendritic cells.[29,30] The process of natural tolerance development occurs in the first years of life, but the sequence of events and the underlying mechanisms are still not understood. By the age of 5 years, 60%—75% of children who are allergic to cow's milk will have become tolerant.[31] Allergy to hen's eggs will resolve in 56%[32] and allergy to peanut in 20% of patients by the age of 3—5 years.[33]

In a study of mice, ingesting pHF-W with limited sensitizing properties reduced the effector response upon whey challenge.[34] This effect is transferable using mesenteric lymph node (MLN) cells and was associated with enhanced $Foxp3^+$ regulatory T cell numbers in the MLN. Therefore, pHF-W retained the capacity to induce active immune suppression in mice, which may be relevant for allergy prevention.[34] Besides, in breast-fed infants with atopy, gut barrier function is improved after cessation of breastfeeding and beginning of hypoallergenic formula feeding with decreased urinary eosinophil protein X, fecal α-1 antitrypsin, and urinary recovery ratio of lactulose and mannitol.[35] After complete cessation of breastfeeding and a shift or partial shift to pHF-W by our study subjects, tolerance is accelerated with better gut barrier function, which might be the underlying cause of the younger age at the last time point when topical corticosteroids were given.

The major limitations of this study were its small sample size and short follow-up period (6 months). Therefore, we reviewed the patients' charts to check the age when the patient was free of topical corticosteroids prescription. Fortunately, we can have correlated data in Fig. 3 and Table 2 showing that the symptoms of AD in the DC group were milder in the first few months, and then nearly the same with the Partial group over the long-term. Regression analysis proved that discontinuing breastfeeding had significant beneficial effect for the last topical corticosteroids age. Some may argue that the PO-SCORAD is less accurate because it is scored by parents instead of an allergist. However, the PO-SCORAD index correlates well with the Scoring Atopic Dermatitis (SCORAD) index, which was validated in Europe (correlation coefficient: 0.79).[36]

The other limitation was the high patient dropout rate (24.1%) at the beginning of the study. Fortunately, we were able to review the patients' charts and found that the 16 infants whose cases were lost to the study were similar to the BM group. This means that these infants' symptoms were not severe enough to cause them to drop out, and thus this should not have a dramatic effect upon our findings.

In summary, the current study demonstrates that exclusive breastfeeding may not be advantageous for all infants, especially for those who develop AD while exclusively breast-fed. In such infants, discontinuing breastfeeding and shifting to pHF-W, or at least partially shifting to pHF-W, might help to improve symptoms and shorten the duration of AD, regardless of sex, age, and parental atopy history.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2017.06.004.

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