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The Efficacy of Oral Immunotherapy in Patients with Cow's Milk Allergy

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ABSTRACT

Cow's milk allergy is the most common type of food allergy that decrease the quality of life of patients and their families. The aim of this study was to evaluate the efficacy of oral immunotherapy in patients with cow's milk allergy.

14 patients above 3 years of age with a history of cow's milk allergy confirmed by positive double blind placebo controlled food challenge (DBPCFC) test, presence of serum IgE against cow's milk and positive SPT (skin prick test) were enrolled in this study. During the immunotherapy all patients received increasing amounts of cow's milk during three phases. The type and severity of allergic reactions were recorded after each dose. The serum IgE and SPT were measured at the beginning and at the end of study.

Since February 2014 to March 2015, 14 patients with the median age of 4.75 (3.7-7) years were studied. 13 patients (92.9%) completed the build up and maintenance phase successfully and became desensitized to cow's milk. During the build up and maintenance phase, 24 (2.0%) and 11 (0.9%) episodes of allergic reactions occurred, respectively. The median serum IgE level against cow's milk proteins and casein decreased from 39.3 to 10.4 and 7.72 to 2.83 (ku/L), respectively. The median of the difference of the wheal diameter in SPT with the control, decreased from 10 to 6 mm during the immunotherapy protocol.

Oral immunotherapy is effective to decrease the frequency and the severity of allergic reactions but due to high rate of allergic reactions and possible anaphylaxis, it must be done under strict supervision of both clinicians and caregivers.

Keywords: Allergy; Desensitizing; Immunology; Immunotherapy; Milk hypersensitivity

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INTRODUCTION

Food allergy is a potentially life-threatening condition with no approved therapies. Up to 12% of parents report different types of adverse food reactions in their children, most of them assumed to be food allergy by parents. Obtaining an accurate estimation of the prevalence and burden of food allergies are hampered, due to lack of uniform, population-based studies that incorporate double blind placebo controlled food challenge (DBPCFC) as the gold standard diagnostic test.[1,2] The reported prevalence of food allergies in studies, which used objective measures is 6% in young children and 3.7% in adults in the USA.[3] Cow's milk allergy is the most common type of food allergies and it affects up to 3% of children less than one year old.[4,5]

Standard treatment for food allergies is the strict avoidance of causative foods.[6-8] This treatment approach decreases the quality of life of patients and their families not only due to dietary restrictions and probable nutritional deficiencies, but also because of severe and life-threatening allergic reactions that might occur due to accidental exposure to allergens.[9-11] New therapeutic approaches for treatment of food allergies have focused on altering the natural course of food allergies, i.e. eliminating allergic reactions, decreasing the severity of the allergic reactions or increase the dose in which the allergic reactions occurs. Most of the studies in this field focused on oral immunotherapy, in which doses of the food protein are given in gradually increasing amounts toward a maintenance dose in order to increase the reactive dose or decrease the severity of allergic reactions in patients.[8,12-16] In most of the cases (85% of patients) cow's milk allergy disappears by the age of 3; however, some of the patients continue to present allergic reactions beyond this age and currently there is no curative procedure for this group.[17-19] Recent studies on oral desensitization in patients with cow's milk allergy have demonstrated hope, with efficacy rate up to 86%.[20-23]

Our aim in this study was to evaluate the efficacy of oral desensitization in children with cow's milk allergy.

MATERIALS AND METHODS

Patient Selection

Patients above 3 years of age with a history of cow's milk allergy that were under supervision for more than 6 months at the Allergy and Immunology Clinic of Children's Medical Center, Tehran, Iran were enrolled in this study. The inclusion criteria were positive history of cow's milk allergy, positive skin prick test (wheal diameter > 3mm larger than saline control), the presence of specific serum IgE (sIgE) against whole cow's milk proteins or any isolated cow's milk proteins i.e. casein, α-lactoglobulin, β- lactoglobulin (sIgE level>0.35 ku/L), and a positive DBPCFC test. The exclusion criteria were poor compliance of patient and his/her caregivers, uncontrolled asthma, cardiovascular disease in which the use of epinephrine is contraindicated, negative skin prick test (SPT), and severe systemic disease. The course of treatment, side effects, research confidentiality and the right of withdrawal during the study were explained to the parents and an informed consent was obtained. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki. Our Institutional Review Board and Ethics Committee approved this study (No: 6211568003-140288). This study was registered in IRCT (IRCT ID: IRCT2015041621793N1)

Methods

DBPCFC Test

All of the patients underwent DBPCFC in which the verum meal consisted of a milk-based formula (BioMeal, Fassbel, Belgium) and strawberry flavor, and the placebo meal consisted of a soy based formula (BioMeal Soy, Fassbel, Belgium) and strawberry flavor. Each of the solutions was tested in separate days and in randomized pattern. Patients had been withdrawn of systematic drugs at least 7 days previously. Initially 3 drops of the solution were put in lower lip fornix and then oral doses of 0.5, 2, 5, 20, 60, 162.5 mL were given every 15 minutes. All of the clinical signs and symptoms that occurred subsequently were recorded carefully by the same physician. Patients were discharged from hospital at least after 6 hours of the termination of the challenge test.

Oral Immunotherapy Protocol

The oral immunotherapy (OIT) in this study consisted of 3 phases; rush, build up and maintenance. During the rush phase (the first day) all of the patients were admitted in the hospital and increasing amounts of milk were administered every 30 minutes (Table 1) under the direct observation.

Patients were discharged from hospital 6 hours after the last dose. During the build up phase (from the second day) the daily dose of milk increased every week. The first dose in each week was administered as inpatient and the remaining doses as outpatient. In this phase patients were discharged 6 hours after the initial dose in each week. For each patient, each of the weekly doses was modified based on the type and severity of allergic reactions that they presented in previous doses. In the maintenance phase, patients, who completed the build up phase successfully, received 200 to 250 mL of cow's milk each day for 90 days. During the build up and the maintenance phases, patients' caregivers were requested to fill a daily form, including information about the time and amount of the daily dose and severity and the onset of signs and symptoms that occurred after the ingestion of the milk. Patients' caregivers were asked to observe the patients at least for an hour after ingestion of the milk and prevent him/her from vigorous physical activity for three hours. All of the caregivers received an action plan, and necessary medications and they were advised to contact us in case of an emergency.

Serum IgE level and Skin Prick Test

sIgE level against casein and cow's milk proteins was measured by the Elisa method with UniCAP 100 system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). An IgE level greater than 0.35 ku/L was considered as positive serology. SPT was performed by cow's milk extract (Greer Laboratories, Lenoir, North Carolina, USA) and results were considered positive when the wheal was at least 3 mm larger than the saline control.

Table 1. The oral immunotherapy protocol of cow's milk allergy

Day	Dose (mL)		Note
	Clinic	Home	
		Rush Phase	
1	0.05	-	Inpatient management, dose interval was 30 minutes
	0.1	-	
	0.3	-	
	0.6	-	
		Build Up Phase	
2-8	1	2	
9-15	5	5	
16-22	10	10	
23-29	20	20	
30-36	40	40	
37-43	60	60	
44-50	100	100	
51-57	150	150	
58-64	200	200	
65-71	250	250	
Total	837	5022	
		Maintenance	
72-162	-	200	
Total	-	18000	

Statistical Analysis

Values were expressed as frequency (number and percentage), and median. Fisher's exact test and chi-square tests were used for 2×2 comparison of categorical variables, whereas Pearson's and Spearman correlation coefficient were calculated for assessment of correlation between quantitative and qualitative variables, respectively. Statistical analyses were performed using the SPSS software package, version 20 (SPSS Inc., Chicago, IL, USA). A *p*-value<0.05 was considered significant.

RESULTS

Since February 2014 to March 2015, 22 patients with a history of adverse food reactions (pruritus, erythema, urticaria, angioedema, perioral dermatitis, atopic dermatitis, vomiting, abdominal pains, diarrhea, rhinoconjunctivitis, asthma and anaphylaxis) after ingestion of cow's milk were enrolled in this study. The most common clinical presentations were rhinoconjunctivitis (59.0%), generalized urticaria (54.5%), cough (31.8%), wheezing (27.3%), and throat pruritus (27.3%). Of these, 2 patients had negative serology and SPT and 6 patients had negative DBPCFC test. 14 patients (10 male and 4 female) were confirmed to have food allergy to cow's milk based on the inclusion criteria. The median age of study population was 4.75 (3.7-7) years and the median follow up period of these patients before the initiation of this study was 14 (6-23) months. 7 (50.0%) patients had history of atopic disease, 8 (57.1%) patients had history of adverse reaction to other foods including fish, egg, tree nuts and peanut and 5 (35.7%) patients had history of allergic reactions due to accidental exposure to cow's milk proteins during the follow up period (Table 2).

Signs and symptoms of patients and the treatment, which is administered for allergic reactions during DBPCFC, rush, build up and maintenance phase are presented in Table 3. The most common clinical presentations during the DBPCFC were rhinoconjunctivitis (57.1%), generalized urticaria (57.1%), cough (50.0%), throat pruritus (35.7%), and wheezing (35.7%). During the DBPCFC all patients were treated with oral antihistamine (diphenhydramine); 6 patients were treated with short-acting β2 agonists spray SABA, salbutamol) and 2 patients received epinephrine due to severe allergic reactions (Table 3).

In build up phase 1190 doses of cow's milk (5859 mL) were administered in 13 patients who completed the build up phase successfully and allergic reactions occurred in 24 (2.0%) doses. A detail of allergic reactions are shown in Table 4. Also, patient No. 9 left the study in the 6th week of build up phase because of severe allergic reactions. The most common clinical presentations in patients who successfully completed the build up phase were, rhinoconjunctivitis (62.5%), cough (58.3%) generalized urticaria (45.8%) and wheezing (29.1%). In all of these episodes, oral antihistamine (diphenhydramine) has been administered; SABA (salbutamoul) was administered in 15 episodes, 3 doses of epinephrine were administered in two episodes of allergic reactions (Table 4).

During the maintenance phase 1170 doses of cow's milk (261000 mL) were administered and 11 (0.9%) episodes of allergic reactions occurred in 9 patients. Two episodes of allergic reactions happened in patient No. 1 and 12. All of the patients were treated with oral anti-histamine (diphenhydramine); patients 3 and 12 received SABA spray (salbutamol) as well. The most common clinical presentations were rhinoconjunctivitis (54.5%) localized urticaria (45.5), and cough (18.2%), data were shown in Table 3. The treatments administered in this study are shown in Table 4.

The results of SPT and serum IgE levels against casein and milk proteins are shown in Table 5. The median of the difference of the wheal diameter with the control, decreased from 10 to 6 mm. After the OIT, the sIgE level of cow's milk proteins and casein decreased from 39.30 to 10.40 and 7.72 to 2.83 (ku/L), respectively (Wilcoxon signed rank test, *p* value=0.002, 0.002, 0.003 respectively).

Table 2. The demographic data and the clinical history of the patients with cow's milk allergy and the results of double blind placebo control food challenge

ID	Sex	Age	Primarily Symptoms	Hx. of atopic disease	Other food allergy	Dur. Of F/U (month)	Accidental exposure	Symptoms during DBPCFC	Dose (mL)
1	M	4	Gen. urticaria, Cough, Wheezing, Rhinoconjunctivitis	Asthma	Egg	8	-	Gen. urticaria, Cough, Wheezing[2]	2
2	F	3.5	Gen. urticaria, Rhinoconjunctivitis	-	-	10	Gen. Urticaria[1]	Gen. Urticaria, Rhinoconjunctivitis[1]	20
3	M	5	Gen. urticaria, Cough, Wheezing, Rhinoconjunctivitis	Asthma	Egg	14	Gen. urticaria, Wheezing, Respiratory distress [3]	Gen. urticaria, Cough, Respiratory distress, Rhinoconjunctivitis[3]	3 Drop
4	M	4.5	Gen. urticaria, Rhinoconjunctivitis	-	Fish	7	-	Gen. urticaria, Rhinoconjunctivitis[1]	60
5	M	5.5	Gen. urticaria, Cough, Wheezing, throat pruritus	-	Tree nuts, Fish	19	(Two episode of) Gen. urticaria, cough, wheezing, rinoconjunctivitis[3]	Gen. urticaria, Cough, Wheezing, throat pruritus, Rhinoconjunctivitis[3]	5
6	F	3.5	Gen. urticaria, Rhinoconjunctivitis	-	Egg, peanut	15	-	Gen. urticaria[1]	60
7	M	5.5	Abdominal pain, Nausea	-	-	14	-	Abdominal Pain, Vomiting[1]	60
8	M	5	Gen. urticaria, Cough, Wheezing, Abdominal pain	Asthma	-	7	Cough, Wheezing[2]	Gen. urticaria, Cough, Wheezing[2]	20
9	M	6	Throat pruritus, Vomiting	Asthma	Fish, Egg	6	-	Throat pruritus, Vomiting[1]	0.5
10	F	7	Cough, Wheezing, Throat pruritus, Rhinoconjunctivitis	Asthma	-	19	-	Cough, Wheezing, Throat pruritus, Rhinoconjunctivitis[1]	5
11	M	4	Gen. urticaria , Rhinoconjunctivitis, Cough	Asthma	Wheat	15	-	Gen. urticaria, Cough, Flashing[2]	5
12	M	3.5	Cough, Wheezing, Rhinoconjunctivitis	Asthma	Egg	9	-	Cough, Wheezing, Rhinoconjunctivitis[2]	2
13	M	5	Rhinoconjunctivitis, Throat pruritus, Sneezing	-	-	14	-	Rhinoconjunctivitis, throat pruritus[1]	60
14	F	4.5	Gen. urticaria, Throat pruritus, Rhinoconjunctivitis	-	-	23	Throat pruritus, Rhinoconjunctivitis[1]	Throat pruritus, Rhinoconjunctivitis[1]	60

DBPCFC, Double blind placebo control food challenge; Hx, History; Dur, Duration; Gen, Generalized. 1-Treatment with oral diphenhydramine, 2-Treatment with oral diphenhydramine and short acting beta-agonist, 3-Treatment with oral diphenhydramine and short acting beta-agonist and single dose of Epinephrine

Table 3. The result oral immunotherapy protocol cow's milk allergy

ID	Build up Period (Weeks)	Dose of Allergic reaction	Allergic reactions during Build up phase	Main. Period	Main. Dose	Allergic reaction (Main. phase)
1	14	10	Gen. urticaria[1]	90	200	-
		60	Loc. urticaria, Cough, Wheezing[2]			
2	12	10	Loc. urticaria[1]	90	250	Loc. urticaria, Rhinoconjunctivitis[1,5]
3	18	2	Gen. urticaria, Cough, Rhinoconjunctivitis[2]	90	200	Cough, Rhinoconjunctivitis, Wheezing[2]
		40	Gen. urticaria, Sneezing , Wheezing, Rhinoconjunctivitis, Respiratory distress[4]			
		100	Gen. urticaria, Rhinoconjunctivitis, Sneezing[1]			
4	10	-	-	90	250	Sneezing, Rhinoconjunctivitiss[1]
5	18	10	Gen. urticaria, Cough, Wheezing[2]	90	200	Loc. urticaria, Throat pruritus[1]
		40	Gen. urticaria, Cough, Rhinoconjunctivitis[2]			
		100	Gen. urticaria, Cough, Rhinoconjunctivitis[2]			
6	10	40	Gen. urticaria, Sneezing, Rhinoconjunctivitis[1]	90	250	Loc. urticaria, Rhinoconjunctivitis[1]
7	10	-	-	90	250	-
8	12	40	Gen. urticaria, Cough[2]	90	250	Loc. urticaria[1]
		150	Loc. urticaria, Cough[2]			
9	10	10	Vomiting, Abdominal pain	-	-	-
10	15	10	Cough, Wheezing[2]	90	200	Sneezing, Rhinoconjunctivitis[1]
		100	Cough, Rhinoconjunctivitis[2]			
		150	Sneezing, Rhinoconjunctivitis[1]			
11	11	5	Gen. urticaria, Cough[2]	90	200	Loc. urticaria[1]
		20	Gen. urticaria, Cough[2]			
		150	Loc. urticaria, Throat pruritus, Rhinoconjunctivitis[1]			
12	20	5	Cough, Rhinoconjunctivitis, Wheezing[2]	90	200	Cough, Rhinoconjunctivitis[2,5]
		60	Cough, Rhinoconjunctivitis, Wheezing[2]			
		100	Cough, Rhinoconjunctivitis, Wheezing, Flashing[3]			
13	10	40	Sneezing, Rhinoconjunctivitis[1]	90	200	-
		100	Sneezing, Throat pruritus, Rhinoconjunctivitis[1]			
14	10	60	Throat pruritus, Rhinoconjunctivitis[1]	90	250	-

Main, Maintenance; Gen, Generalized; Loc, Localized. 1-Treatment with oral diphenhydramine, 2-Treatment with oral diphenhydramine and short acting beta-agonist. 3-Treatment with oral diphenhydramine and short acting beta-agonist and single dose of Epinephrine, 4- Treatment with oral Diphenhydramine and Short Acting Beta-Agonist and two doses of Epinephrine and admission, 5-Two Episode of allergic reactions

Table 4. The treatments during each phase of oral immunotherapy of cow's milk allergy

	Diphenhydramine	SABA	Epinephrine	Admission
DBPCFC[+]	14	6	2	0
Build up[*]	24	15	2	1
Maintenance	9	2	0	0
Total	47	23	4	1

SABA, Salbutamol; DBPCFC, Double blind placebo controlled food challenge.

Table 5. The result of skin prick test, and serum level of specific Cow's milk and casein IgE

ID	Sex	Age	SPT before OIT	SPT after OIT	sIgE (Milk) before OIT	sIgE (Milk) after OIT	sIgE (Casein) before OIT	sIgE (Casein) after OIT
1	M	4	15	12	12.20	3.45	8.21	5.20
2	F	3.5	7	6	3.82	2.75	0.42	1.20
3	M	5	18	12	48.20	18.20	18.45	16.95
4	M	4.5	7	4	19.9	Undetected	0.45	0.35
5	M	5.5	10	6	>100	84.9	3.99	2.83
6	F	3.5	5	4	31.6	9.3	0.48	0.35
7	M	5.5	8	6	19.2	19.2	10.0	0.89
8	M	5	15	11	83.5	10.7	7.24	3.99
9	M	6	10	Discontinue	31.5	Discontinue	2.78	Discontinue
10	F	7	10	6	>100	83.4	13.1	6.01
11	M	4	10	10	>100	Undetected	10	0.89
12	M	3.5	8	5	>100	90.4	2.96	0.45
13	M	5	12	7	83.5	10.4	13.10	6.01
14	F	4.5	9	5	14.70	6.88	9.47	6.02

sIgE, Specific immunoglobulin E; SPT, Skin prick test; OIT, Oral immunotherapy.

DISCUSSION

The only accepted treatment for food allergy is the complete avoidance of causative allergen.[8,17] But some of the patients continue to have allergic reactions beyond early childhood. In these patients, food elimination diet significantly decreases the quality of life of both patients and their families due to malnutrition, eating disorder and psychological problem as well as accidental exposure to cow's milk and anaphylactic reactions which is followed.[8,24,25] In addition, the elimination of cow's milk from the diet is difficult, because it could be hidden and not necessarily labeled in some products. Many efforts have been conducted to find alternative treatments that change the natural course of food allergies. Among them, OIT is one of the mostly investigated.[11,20,21,23,26-42]

In some studies such as Patriarca et al. and Meglio et al. oral sodium cromoglycate and cetirizine are used as premedication but in our study in order to achieve a better knowledge of the clinical presentation and side effects during OIT no premedication have been used.[21,29,39] During desensitization protocol, increasing amounts of cow's milk are given and allergic reactions

would be treated properly if occurred.[11,20,23,26,31,33-36,39-42] Our study consists of three phase, rush, build up and maintenance. During the rush phase, the cow's milk protein is introduced in the patient's diet, during the build up phases the daily dose of milk is increased up to 200 to 250 mL and during the maintenance phase, 200 to 250 mL of cow's milk is given every day. In this study, during the build up and maintenance phase allergic reactions occurred in 2.0% and 0.9% of doses. The most common clinical presentations were rhinoconjunctivitis, cough and urticaria. Most of the allergic reaction in build up and maintenance phases were mild and have been controlled with oral antihistamine. SABAs were administered for 15 allergic episodes in build up phase and for 2 episodes in maintenance phase. Moreover, 2 patients needed to be treated with intramuscular epinephrine in the build up phase (one of them received 2 doses). During the follow up period before the initiation of this study, 6 episodes of allergic reaction occurred in these patients and in three episodes they were treated with intramuscular epinephrine. These results and the result of similar studies show that the rate of allergic reaction is higher in OIT, but the severity of them is much lower. Therefore, OIT is a relatively safe approach if being performed with necessary cautions.[20-22,27,28,31,32,34,36,37,41-43]

13 (92.9%) out of 14 patients in this study completed the build up and maintenance phases successfully and became desensitized to cow's milk. One patient dropped out of the study in 6th week of the build up phase due to severe abdominal pain and vomiting. In the study by Patriarca et al. 6 patients with a history of cow's milk allergy were studied. The OIT protocol started with 0.3 mg of cow's milk protein and increased to 120 mL of whole milk on day 104. Oral soudium cromoglycate was administered prior to Cow's milk ingestion at the beginning of the treatment. OIT was successful in 4 (66.7%) of the 6 patients.[29]

Meglio et al. studied 21 patients with at least 6 years of age, whose allergies to cow's milk had been confirmed with DBPCFC. The starting doses were 0.06 mg of cow's milk protein and OIT protocol lasted 6 months. 15 (71.4%) out of 21 patients achieved a daily intake of 200 mL and 3 patients tolerated a daily intake of 40 to 80 mL of whole cow's milk.[21] Longo et al. studied 60 patients older than 5 years old patients with history of severe allergic reactions to cow's milk, high level of serum specific cow's milk proteins (CMPs)-IgE and positive DBPCFC with small amount of milk. These patients had been randomly divided into two equal groups. Patients who underwent OIT received antihistamine treatment during hospital admission and in home until a daily dose of 150 mL reached, and then it was reduced over 4 weeks. 11 (36.7%) patients who underwent OIT reached a daily intake of 150 mL or more and 16 patients could tolerate 5 to 150 mL of cow's milk. None of the patients in control group developed tolerance spontaneously.[20] In another study Alvaro et al. studied 66 patients with cow's milk allergy, confirmed by DBPCFC. 44 patients were anaphylactic and 22 patients were non-anaphylactic. The OIT protocol was started with 4 mL of cow's milk and was increased up to 200 mL. In non-anaphylactic group 16 (72.7%) patients and in anaphylactic group 35 (79.6%) patients became desensitized. Moreover, Cow's milk-specific IgE levels and caseinspecific IgE levels were significantly lower in the tolerant patients at baseline.[43]

In our study 13 (92.9%) out of 14 patients completed the OIT protocol successfully. The higher success rate in our study could be due to lower age of studied population. In addition, the higher rate of allergic reactions was due to avoidance of premedication in our study in comparison with other studies.[20,21,29] Moreover, in our study the cow's milk and casein specific IgE levels dropped significantly. While in other studies by Elizur et al., Ito et al., and Savilahti et al. high level of cow's milk specific sIgE and larger wheal size in SPT was associated with increased risk of persistent cow's milk allergy.[17,44,45] Therefore by decreasing the serum levels of these antibodies and wheal size, OIT might accelerate the improvement of cow's milk food allergy.[17,44,45] We know that the weak points of our study is a lack of control group, thus a control group is needed to see better the efficacy of the protocol. However, we were disabling to perform a randomized double-blind placebo control trail for evaluating the efficacy of oral immunotherapy, because almost all of the patient's caregivers disagreed with this type of study and requested that their child be placed in the treatment group. The result of this study and other studies show that OIT is effective to decrease the frequency and the severity of allergic reactions, as well as in changing the natural course of cow's milk allergy by altering the IgE

profile but due to high rate of allergic reactions and possible anaphylaxis it must be done under an strict supervision of both clinicians and caregivers.

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