

Successful management of severe cow's milk allergy with omalizumab treatment and CD-sens monitoring

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Food allergy is common in children and young adults and may be difficult to diagnose and is at present treated with avoidance of the food in question. The aim of this report is to share our clinical experiences monitoring omalizumab treatment by basophil allergen threshold sensitivity, CD-sens. Five children, 6–16 years of age, with a severe milk allergy including episodes of anaphylaxis and IgE-antibodies, between 30 and 160 kU_A/L to casein and alpha-lactalbumin (milk proteins), were treated with omalizumab. CD-sens, was tested prior to and after 4 months of omalizumab and if turned negative, it was followed by an oral milk challenge. All children became negative in CD-sens and had a negative milk challenge, but one child required doubling of the omalizumab dose to achieve a negative CD-sens before a challenge was done. Omalizumab appears useful in treatment of severe food allergy, e.g., anaphylaxis to milk, and CD-sens monitoring may decide when and how to perform a food challenge.

Key words: Basophil; Food hypersensitivity; Anaphylaxis; Child; Omalizumab

INTRODUCTION

Food allergy is common in children and young adults [1] and has a great impact on daily life of the child and family. Symptoms of food allergy can be potentially life-threatening and an adrenalin auto-injector must always be at hand.

Case history supported by skin- or blood tests and oral challenges will result in a reliable food allergy diagnosis but establishment of the degree of allergen sensitivity is not easily achieved since the reproducibility of a food challenge does not allow determination of the degree of allergen sensitivity [2]. However, basophil allergen threshold sensitivity, CD-sens

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[3], is a safe, fast, and inexpensive approach to get a quantitative measure of the patient's allergen sensitivity in allergic asthma [4] and food allergy [5].

Treatment of food allergy is usually based on avoidance of exposure and equipping patients with an adrenaline device and management plan. Omalizumab, (Xolair, Novartis AG, Basel, Switzerland), registered for treatment of allergic asthma, has recently been used to treat IgE-mediated food allergy [6, 7].

The aim of this report is to share our clinical experiences monitoring omalizumab treatment by basophil allergen threshold sensitivity, CD-sens, in a few severely milk allergic patients.

CASE REPORT

This is a description of 5 children, 6–16 years of age, with a milk allergy diagnosed following severe reactions including anaphylaxis, graded after the European Academy of Allergy and Clinical Immunology position paper [8], and IgE-antibodies (IgE-ab) between 30 and 160 kU_A/L to casein and alpha-lactalbumin (milk proteins). In addition they all had moderate to severe atopic eczema and allergic asthma and rhino-conjunctivitis, and reactivity to other allergens. They were treated with inhaled steroids, long-acting β -2 agonist, montelukast, antihistamines, topical steroids, tacrolimus and antihistamines and all carried an adrenalin auto-injector. An oral milk challenge was considered too risky due to previous severe anaphylactic reactions with symptoms including loss of consciousness, apnea and cyanosis.

All subjects gave their informed consent to participate in this case report.

Serum concentrations of IgE (kU/L) were determined by ImmunoCAP Total IgE and of IgE-ab (kU_A/L) to the milk proteins casein and alpha-lactalbumin by ImmunoCAP Specific IgE

(Thermo Fisher Scientific, Uppsala, Sweden) according to the manufacturer's instructions.

Milk allergen sensitivity was measured by basophil allergen threshold sensitivity, CD-sens after incubation with serial dilutions [3], of casein 0.01–1000 μ g/mL (CAS 9000-71-9) (Sigma-Aldrich Co., St. Louis, MO, USA) or alpha-lactalbumin 0.01–1000 ng/mL (CAS 9051-29-0) (Sigma-Aldrich Co.). CD-sens is defined as the inverted value for the allergen dilution giving a 50% of maximum basophil triggering, measured as CD63% expression, multiplied by 100 [3]. Due to insufficient standardization of the allergen preparations, the CD-sens value cannot be compared between different allergens but can for each allergen be compared between patients and samples.

Omalizumab was provided according to the doses recommended for allergic asthma i.e., based on serum IgE concentration and the patients' body mass. CD-sens to casein and alpha-lactalbumin was measured before start of omalizumab treatment and repeated after 16 weeks. If CD-sens turned negative an oral challenge was performed. Omalizumab treatment was then continued for several years at the lowest dose (75 mg/4 wk) to allow introduction of milk into the daily diet and for immunological tolerance to milk to be achieved.

A milk challenge was performed, in principle following the national Swedish protocol [9], with fresh milk in increasing amounts every 30 minutes starting with 0.05–0.1 mL ending with 50 mL or more. After a successful milk challenge, milk was introduced and regularly consumed.

All patients had a complex clinical picture with severe asthma and rhino-conjunctivitis caused by inhalant allergens. In addition all of them had experienced anaphylactic or repeated severe allergic reactions to milk (Table 1) within 2–3 years before the study and were highly IgE-sensitized to milk proteins.

CD-sens to casein and alpha-lactalbumin was measured before

Table 1. Clinical data on the five patients

Patient	Sex	Age at start of omalizumab (yr)	Symptoms at reaction	Negative oral challenge dose (mL milk)	Allergy to other foods and inhalants
1	Female	15	UR, AS, AP, CY	450	Yes
2	Female	10	UR, VO, AP	160	Yes
3	Male	6	VO, UR, UN	160	Yes
4	Male	16	UR, AS, VO, AP, CY	50	Yes
5	Male	16	VO, UR, AS, CY	200	Yes

All patients had experienced grade III anaphylactic reactions. UR, urticarial; AS, asthma; AP, apnea; CY, cyanosis; VO, vomiting; UN, unconsciousness.

Table 2. Monitoring of omalizumab treatment of milk allergic children with basophil allergen threshold sensitivity, CD-sens

Patient	Before treatment				After treatment			
	IgE (kU/L)	IgE-antibodies		CD-sens	Omalizumab 1		Omalizumab 2	
		Allergen	kUA/L (%)		Dosage	CD-sens	Dosage	CD-sens
1	1,700	Alpha-lact	19 (1.0)	40	600 mg/2 wk	0		
		Casein	66 (3.5)	50				
2	460	Casein	30 (6.5)	123	300 mg/2 wk	0		
3	720	Casein	63 (8.8)	244	225 mg/2 wk	0		
4	400	Alpha-lact	42 (11)	96	450 mg/4 wk	6.4	450 mg/2 wk	0
		Casein	160 (40)	0.7				
5	1,500	Alpha-lact	8 (<1)	19	600 mg/2 wk	0		
		Casein	69 (4.5)	850				

IgE-antibody (IgE-ab) values in kUA/L and in percentage of IgE (IgE-ab/"total IgE").
 CD-sens figures for alpha-lactalbumin (alpha-lact) and casein cannot be compared.

start of omalizumab treatment and repeated after 16 weeks. In patient 1, 2, 3, and 5 CD-sens became negative and, when performed the oral milk challenge was negative while patient 4 still had a positive CD-sens to alfa-lactalbumin after the initial omalizumab treatment (Table 2). The omalizumab dosage was doubled and when CD-sens was retested after another 16 weeks it was negative and this child also had a negative milk challenge.

In most patients their asthma, rhino-conjunctivitis and atopic eczema improved and their asthma medication could be reduced or even ceased.

DISCUSSION

We describe our clinical experience with treating five multiallergic children suffering from a severe IgE-mediated milk allergy, who had experienced one or several anaphylactic reactions to milk. A pretreatment challenge was considered too risky but the degree of their milk allergen sensitivity was tested by CD-sens. CD-sens has been shown to be an excellent mirror of the allergen sensitivity in the shock organ, e.g., in allergic asthma [4] but also in allergic rhinitis [3] and food allergy [5]. We have previously shown that there is an excellent correlation between positive/negative DBPCFC (double-blind, placebo-controlled food challenge) and CD-sens for peanut [5] thus making it possible to avoid food challenges in children with alarming history of food allergy and instead run a harmless basophil stimulation *in vitro* for diagnosis and treatment follow-up.

It was decided to treat the patients with omalizumab, a drug registered for treatment of severe allergic asthma that has also been tried in food allergy [6, 7]. Our experience from treating these five patients indicates that this approach is promising. When CD-sens became negative the oral milk challenge was negative in all patients. However, in the patient with highest percentage (IgE-ab/"total IgE") of IgE-ab to alpha-lactalbumin (11%) and casein (40%) the drug dose recommended for allergic asthma was not high enough to turn CD-sens to alpha-lactalbumin negative [10, 11] and since he was not symptom free and had such an alarming case history it was considered unethical to perform a challenge. Thus, it was decided to double the dose (still within the maximal dose allowed; 600 mg every 2 weeks) and when CD-sens to both alpha-lactalbumin and casein became negative the milk challenge was performed and was negative. The negative casein CD-sens already at the low omalizumab dose, despite the high level of IgE-ab, might be due to presence of casein allergen binding factors [12] or heterogeneity of the allergen.

Based on the effect on the IgE-mediated allergy in the patients reported, our study supports previous reports of the utility of omalizumab in severe food allergy [6, 7]. However, we propose that CD-sens is used to determine the effect of treatment and to guide timing of challenges to avoid reactions. This approach will reduce the risks of oral food challenges. However, CD-sens monitoring will also reduce high numbers of omalizumab nonresponders [11] reported since the dosages can be adjusted according to the patient's CD-sens results.

The effect of omalizumab on IgE-mediated food allergy is promising. In view of ongoing trials with oral immunotherapy in severe food allergy [13-15] and their appreciable risks we are, however, eager to report these data since using omalizumab and monitor the effect with CD-sens provide a safe alternative.

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