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

Caroline Nilsson1, Lennart Nordvall2, S.G.O. Johansson3, and Anna Nopp3,*

1Department of Clinical Science and Education, Södersjukhuset, Centre for Allergy Research, Karolinska Institutet and Sach’s Children’s Hospital, Södersjukhuset, 118 83 Stockholm, Sweden
2Department of Women’s and Children’s Health, Uppsala University Hospital, 751 85 Uppsala, Sweden
3Department of Medicine, Clinical Immunology and Allergy Unit, Karolinska Institutet and University Hospital, 171 76 Stockholm, Sweden

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/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.

Correspondence: Anna Nopp
Clinical Immunology and Allergy Unit, Karolinska University Hospital, Solna L2:04, SE-171 76 Stockholm, Sweden
Tel: +46 8 517 767 12
Fax: +46 8 33 57 24
E-mail: anna.nopp@ki.se

Received: May 14, 2014
Accepted: September 26, 2014

This is an Open Access article distributed under the terms of the Creative Commons Attribution. Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

http://apallergy.org
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/L to casein and alpha-lactalbumin (milk proteins). In addition they all had moderate to severe atopic eczema and allergic asthma and rhinoconjunctivitis, and reactivity to other allergens. They were treated with inhaled steroids, long-acting β-2 agonist, montelucast, 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/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 of casein 0.01–1000 µg/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 rhinoconjunctivitis 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

| 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 |

Table 1. Clinical data on the five patients

All patients had experienced grade III anaphylactic reactions.

UR, urticarial; AS, asthma; AP, apnea; CY, cyanosis; VO, vomiting; UN, unconsciousness.
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 alpha-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.

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

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

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

REFERENCES

1. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA. ICON: food allergy. J Allergy Clin Immunol 2012;129:906-20.
2. Glaumann S, Nopp A, Johansson SG, Borres MP, Nilsson C. Oral peanut challenge identifies an allergy but the peanut allergen threshold sensitivity is not reproducible. PLoS One 2013;8:e53465.
3. Nopp A, Johansson SG, Ankerst J, Bylin G, Cardell LO, Gronneberg R, Irander K, Palmqvist M, Oman H. Basophil allergen threshold sensitivity: a useful approach to anti-IgE treatment efficacy evaluation. Allergy 2006;61:298-302.
4. Dahlen B, Nopp A, Johansson SG, Eduards M, Skedinger M, Adejoyin J. Basophil allergen threshold sensitivity, CD-sens, is a measure of allergen sensitivity in asthma. Clin Exp Allergy 2011;41:1091-7.
5. Glaumann S, Nopp A, Johansson SG, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. Allergy 2012;67:242-7.
6. Rafi A, Do LT, Katz R, Sheinkopf LE, Simons CW, Klaustermeyer W. Effects of omalizumab in patients with food allergy. Allergy Asthma Proc 2010;31:76-83.
7. Lieberman JA, Chehade M. Use of omalizumab in the treatment of food allergy and anaphylaxis. Curr Allergy Asthma Rep 2013;13:78-84.
8. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, Moneret-Vautrin A, Niggemann B, Rance F; EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007;62:857-71.
9. Komjölsprovokation [Internet]. Swedish Pediatric Society, Section of Allergy; 2011 [cited 2014 Jun 1]. Available from: http://www.barnallergisektionen.se/stenciler_nya06/c6%20fodoamnesprov.pdf.
10. Johansson SG, Nopp A, Oman H, Ankerst J, Cardell LO, Gronneberg R, Matsols H, Rudblad S, Strand V, Stalenheim G. The size of the disease relevant IgE antibody fraction in relation to ‘total-IgE’ predicts the efficacy of anti-IgE (Xolair) treatment. Allergy 2009;64:1472-7.
11. Lafeuille MH, Gravel J, Zhang J, Gorsh B, Figliomeni M, Lefebvre P. Association between consistent omalizumab treatment and asthma control. J Allergy Clin Immunol Pract 2013;1:51-7.
12. Nopp A, Cardell LO, Johansson SG, Oman H. CD-sens: a biological measure of immunological changes stimulated by ASIT. J Allergy Clin Immunol 2013;64:811-4.
13. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow’s milk allergy. J Allergy Clin Immunol 2011;127:1622-4.
14. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, Palmer C, Deighton J, Ewan P, Clark A. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet 2014;383:1297-304.
15. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol 2013;132:1368-74.