

Xolair Is Effective in Allergics with a Low Serum IgE Level

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Key Words

CD-sens • Low IgE level • Basophil • IgE antibody

Abstract

Background: Two atopic patients suffering from severe allergy difficult to handle by conventional medication were given Xolair despite an IgE level <30 kU/l. **Methods:** Increasing dosages were given and monitored by clinical evaluation and CD-sens to clinically relevant allergens. The patients' IgE antibody fractions were 11–14%. **Results:** Xolair dosages extrapolated from a recommended dose for IgE of 30–75 kU/l were adapted to the patients' IgE body pool but had very little effect. The double dose resulted in some clinical improvement and a decrease in CD-sens. However, not until the dose was doubled again did the patients become symptom free, although 1 patient needed some additional drugs but no oral steroids. CD-sens turned negative to 5 of the 7 tested allergens. **Conclusions:** Xolair is most useful also in atopics with an IgE level <30 kU/l. The dose must be adjusted to the size of the IgE antibody fraction adding all non-cross-reacting, clinically relevant specificities.

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Introduction

For several years, a humanized monoclonal anti-IgE antibody, omalizumab, (Xolair, Novartis, Basel, Switzerland) has been an alternative treatment for moderate to severe IgE-mediated allergic asthma. Xolair is not registered for use in patients with a low serum IgE concentration (<30 kU/l) [1] which is difficult to understand, since many atopics with severe, allergic problems have such low levels. These patients are likely to need limited dosages of Xolair in contrast to patients with high levels of serum IgE (>700 kU/l). On the other hand, in patients with low concentrations, the clinically relevant IgE antibody fraction might be quite large, which might be a problem in reaching the optimal dosage of Xolair [2].

We discuss 2 patients with pronounced IgE-mediated asthma and rhinoconjunctivitis that, despite heavy medication, needed hospitalization, and thus, really could benefit from Xolair treatment. Although both had a serum IgE concentration <30 kU/l, it was decided, for clinical reasons, to treat them with Xolair and to monitor the effect on their clinical and immunological parameters of IgE-mediated allergy.

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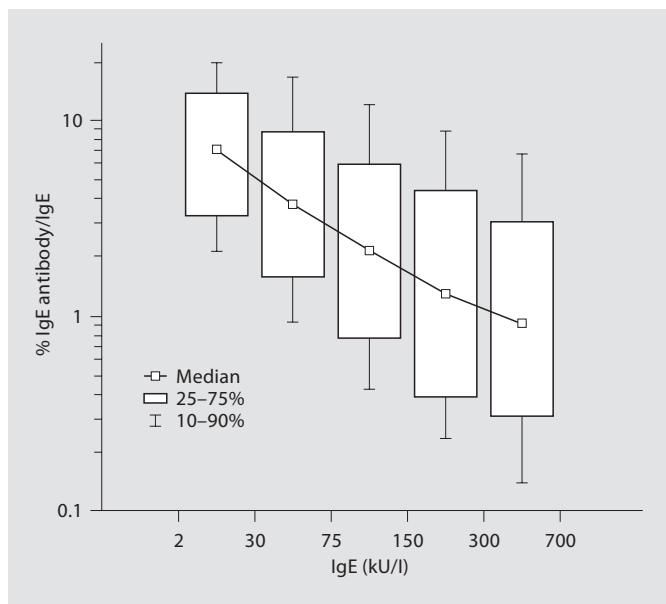


Fig. 1. IgE antibodies to cat (e1) as percentage of IgE in different serum IgE dose ranges in all serum samples sent to the Allergy Laboratory, Karolinska University Hospital, Stockholm, during the period 2003–2005, fulfilling the following criteria: age >12 years, having a serum IgE concentration of 2–700 kU/l and being tested for IgE antibodies to cat. In the low, 2–30 kU/l, IgE group, 151 (14.5%) had a positive (<0.35 kU_A/l) IgE antibody test to cat. The results for the interval 30–700 kU/l have been published previously [3].

Material and Methods

Patients

Patient 1 is a woman born in 1968. Since childhood she had suffered from severe allergic asthma, rhinoconjunctivitis and atopic eczema with 2+ to 4+ skin prick tests to many inhalant and food allergens and corresponding IgE antibodies (0.39–0.84 kU_A/l), which, however, represented a large fraction of her low IgE level (13.8 kU/l). She was taking antihistamines, leukotriene receptor antagonists, inhaled steroids at a high dose, long-acting β -agonists, antihistamine eye drops, nasal steroids and now and then oral steroids. Occasionally she was hospitalized. In April 2007, she had to visit the emergency clinic 3 times. One attempt to start her on allergen-specific immunotherapy (ASIT) had to be stopped due to severe local and general side effects.

Patient 2 is a man born in 1969. At the age of 19, allergic asthma and rhinoconjunctivitis due to birch pollen became a problem. Later, he developed a pronounced allergy to cat and a mild allergy to dog. In early 2008, he had 1+ to 2+ skin prick tests to birch and grass pollen and to dog and cat dander and IgE antibodies in the order of 0.20–0.92 kU_A/l, which represented a large percentage of his IgE level (13.3 kU/l). He was given antihistamines and inhaled steroids at a high dose which kept his symptoms under control. ASIT has been discussed but never started.

Due to their considerable allergy problems, both were eager to try the anti-IgE immunomodulation therapy with omalizumab (Xolair, Novartis, Basel, Switzerland).

Data

Results from the Allergy Laboratory, Karolinska University Hospital, Stockholm, of samples analyzed for IgE and IgE antibodies to cat dander with a serum IgE level of 2–30 kU/l (interval 30–700, as previously published [3]), were calculated from existing files.

Basophil Analyses

The patients' allergen sensitivity, CD-sens [4, 5], and the number of IgE and Fc ϵ RI molecules per basophil [2] were calculated as described.

Immunoglobulin Analyses

The serum concentrations of IgE and IgE antibodies, using 0.1 kU_A/l as a cut-off, were determined by ImmunoCAPTM (Phadia AB, Uppsala, Sweden) according to the manufacturer's instructions. The relative IgE antibody concentration was expressed as absolute value in percentage of IgE.

Results

Patient Characteristics

Serum samples drawn in April 2008 showed that patient 1 had a serum IgE level of 13.8 and patient 2 of 13.3 kU/l. The IgE antibody concentrations for patients 1 and 2 were low: birch 0.17 kU_A/l (1.2% of IgE) and 0.9 kU_A/l (6.8%); timothy 0.31 kU_A/l (2.2%) and 0.26 kU_A/l (2.0%); cat 0.86 kU_A/l (6.2%) and 0.30 kU_A/l (2.3%); mite 0.6 kU_A/l (4.3%) and <0.1 kU_A/l, respectively. However, added together, they reached 13.9% for patient 1 and 11.1% for patient 2.

In cat-sensitized patients with an IgE level <30 kU/l (fig. 1), the median cat IgE antibody fraction was 7.3% (data for 30–700 kU/l [3]). A total of 1,041 of 4,466 sera (23.3%) tested for IgE antibodies to cat belonged to this group, and of those, 151 (14.5%) were positive (>0.35 kU_A/l). The figure for mite was 8.3%.

IgE and Fc ϵ RI on Basophils

Since the patients had an IgE body pool of approximately 50% of those in the lowest interval, treatment was started with 75 mg Xolair per month, i.e. half the recommended dose. After 4 months, the number of basophil IgE molecules and Fc ϵ RI dropped 4–10 fold (table 1).

After 3 months with the double dose (150 mg), the number of IgE molecules on the basophils was unchanged, while Fc ϵ RI had further dropped approximately 3 fold in patient 1 and 2 fold in patient 2 (table 1).

Table 1. IgE and FcεRI on basophils and CD-sens to the clinically relevant allergens in relation to timing and dosage of Xolair

Months with Xolair	CD-sens birch	CD-sens timothy	CD-sens cat	CD-sens mite	IgE per cell	FcεRI per cell
Patient 1						
0	0.4	0.6	23	0.4	28,400	15,200
2	0.4	1.0	12	0.1	6,400	3,000
4	0.1	3.9	16	0.1	6,200	4,100
7	0	0.2	1.2	<0.1	8,300	1,500
10	0	0	1.4	0	400	1,800
Patient 2						
0	3.5	0.5	5.8	NS	24,900	10,900
2	2.0	1.6	5.8	NS	1,800	2,600
4	1.2	1.9	5.0	NS	2,300	2,300
7	0.8	0.5	0.6	NS	3,400	1,200
10	0.2	0?	0?	NS	800	2,000

NS = Not sensitized. The initial dose (75 mg) was doubled to 150 mg at 4 and to 300 mg at 7 months. The responses of the basophils in the 10-month sample of patient 2 were very low, and for timothy and cat, 1 duplicate was negative and 1 was weakly positive.

Since both patients still had reactive basophils, it was decided to again double the dose, i.e. to 300 mg. After 3 months, the IgE molecules dropped to 2–3%, while 12–18% of FcεRI were left (table 1).

Symptoms and Medication

Already during the initial dose the patients felt better and could reduce medication. After 4 months, i.e. by end of August, right after the grass pollen season, patient 1 showed a 6-fold and patient 2 a 4-fold increase in CD-sens to timothy (fig. 2) but no increase in CD-sens to the other allergens (table 1). Patient 1 had to continue with her medication but did not need oral steroids. Patient 2 had mild symptoms during the pollen season and took antihistamines occasionally.

During the 150-mg period, the symptoms more or less disappeared for both patients and the need for allergy drugs decreased further. However, patient 1 had to continue, and her CD-sens was still weakly positive to cat, and although patient 2 had problems only with cat, he was positive in CD-sens to all 3 allergens (table 1).

During the third 300-mg period, they improved further. Patient 1 continued with lower doses of the drugs while patient 2 had no symptoms or allergy medication. Patient 1 still had a weakly positive CD-sens to cat and

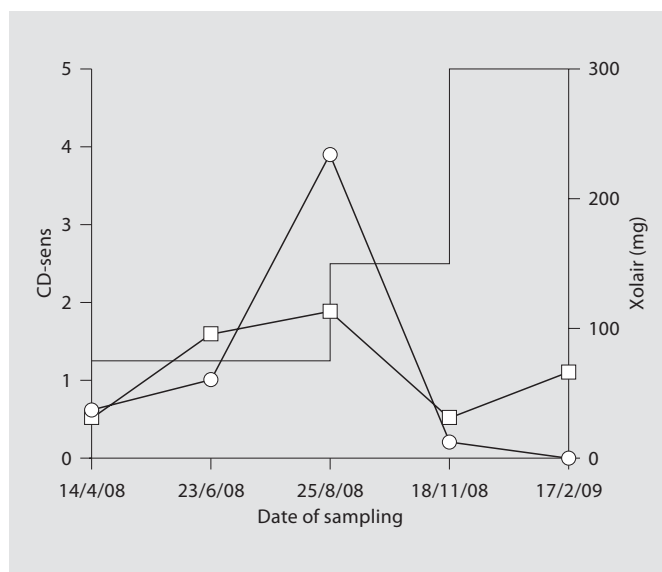


Fig. 2. Seasonal variations in CD-sens to timothy in patient 1 (○) and patient 2 (□) during the Xolair treatment period. Note the increase, most likely due to allergen stimulation, in CD-sens to timothy during the summer.

patient 2 approximately 6% left of his CD-sens to birch (table 1). The response of the basophils of patient 2 to timothy and cat was so low that no accurate calculations could be performed. All other CD-sens tests were negative.

Discussion

The idea behind the treatment of allergy with omalizumab is to eliminate circulating IgE and thereby disease-relevant IgE antibodies which results in a prominent drop in FcεRI receptors on basophils and mast cells [1]. This drop in FcεRI receptors might explain why omalizumab is effective in the chronic urticaria caused by IgG autoantibodies to the receptors [6]. Omalizumab is not registered for allergic asthma in patients with a serum IgE level <30 kU/l, possibly because in the initial report of patients with bronchial hyper-reactivity, none had such low IgE concentrations [7]. However, such patients are not rare. Among sera sent to the Allergy Laboratory at Karolinska University Hospital [3], with suspected cat or mite allergy and with a 'total IgE' level <30 kU/l, 14.5% were positive to cat and 8.3% to mite.

Omalizumab has been found to be less effective in patients with an IgE level <75 kU/l [8], most likely due to a

large IgE antibody fraction (fig. 1), since Xolair is only effective in patients with a low percentage ($\leq 1\%$) of IgE antibodies [2]. In addition, all IgE antibodies to non-cross-reacting allergens that the patient could be simultaneously exposed to must be included in the IgE antibody fraction [9].

We analyzed 2 patients with a long history of pronounced IgE-mediated allergy, low IgE levels (13–14 kU/l) and low (0.1–0.9 kU_A/l) concentrations of disease-relevant IgE antibodies. However, added together, they represented 11–14% of the ‘total IgE’, i.e. much higher than the 3.8% for nonresponders [2]. For clinical reasons, it was decided to give them Xolair. The effect was monitored by clinical evaluation and CD-sens [2, 4]. For the first 4 months, the patients were given a dose extrapolated from the recommendations by Novartis, i.e. half that of the 30- to 75-kU/l group. Although the number of basophil IgE molecules and Fc ϵ RI decreased, the effects on clinical improvement and CD-sens were small (table 1). In addition, the grass pollen season boosted a 4-fold increase in CD-sens to timothy (fig. 2) in patient 1 and a 2-fold increase in patient 2, while CD-sens to the other allergens continued to drop, but slowly.

The dose of Xolair was doubled which resulted in a further, but small, drop in Fc ϵ RI and the number of IgE molecules on the basophils (table 1). The allergy improved, but the patients still had to take drugs and CD-sens to cat was still positive: 1.2 in patient 1 and 0.6 in patient 2.

Thus, the Xolair dose was doubled again to 300 mg per injection, i.e. 4-fold the recommended dose, for another 3 months. As a result, the number of Fc ϵ RI levelled out at 2,000 per basophil, and the number of IgE molecules was very low (400 and 800, respectively; table 1), and although CD-sens to cat in patient 1 was still moderate (1.4), clinically, both patients were now in good condition.

In conclusion, many atopic patients with a ‘total IgE’ level <30 kU/l are suffering from severe, IgE-mediated allergy and need Xolair. However, their IgE antibody fraction, considering the additive effect, is often very large, requiring higher dosages. In the present study, 2 patients with pronounced allergy, low IgE and a large disease-relevant IgE fraction were successfully treated with Xolair. However, the dosage had to be increased to 4-fold that recommended for patients with their IgE body pool. Even though the long-term effect of Xolair seems to be very beneficial, followed by a withdrawal without side effects or rebound phenomena [10], the introduction of ASIT, monitored by CD-sens [11], under Xolair protection [12], could be considered.

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References

- 1 Xolair (omalizumab), summary of product characteristics. <http://www.emea.eu.int/humandocs/PDFs/EPAR/Xolair/H-606-PI-en.pdf>.
- 2 Johansson SGO, Nopp A, Öman H, Ankerst J, Cardell LO, Grönneberg R, et al: The size of the disease relevant IgE antibody fraction in relation to ‘total-IgE’ predicts the efficacy of anti-IgE (Xolair®) treatment. *Allergy* 2009;64:1472–1477.
- 3 Johansson SGO, Öman H, Nopp A, Pettersson S: The importance of IgE antibody levels in anti-IgE treatment. *Allergy* 2006;61:1216–1219.
- 4 Nopp A, Johansson SGO, Ankerst J, Bylin G, Cardell LO, Grönneberg R, et al: Basophil allergen threshold sensitivity. A useful approach to anti-IgE treatment efficacy evaluation. *Allergy* 2006;61:298–302.
- 5 Johansson SGO, Nopp A, van Hage M, Olofsson N, Lundahl J, Wehlin L, et al: Passive IgE-sensitization by blood transfusion. *Allergy* 2005;60:1192–1199.
- 6 Kaplan AP, Greaves M: Pathogenesis of chronic urticaria. *Clin Exp Allergy* 2009;39:777–787.
- 7 Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD: Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991;325:1067–1071.
- 8 Bousquet J, Rabe K, Humbert M, Chung KF, Berger W, Fox H, Ayre G, Chen H, Thomas K, Blogg M, Holgate S: Predicting and evaluating response to omalizumab in patients with severe allergic asthma. *Respir Med* 2007;101:1483–1492.
- 9 Nopp A, Johansson SGO, Lundberg M, Öman H: Simultaneous exposure of several allergens has an additive effect on multisensitized basophils. *Allergy* 2006;61:1366–1368.
- 10 Nopp A, Johansson SGO, Ankerst J, Palmqvist M, Öman H: CD-sens and clinical changes during withdrawal of Xolair after 6 years of treatment. *Allergy* 2007;62:1175–1181.
- 11 Nopp A, Cardell LO, Johansson SGO, Öman H: CD-sens: a biological measure of immunological changes stimulated by ASIT. *Allergy* 2009;64:811–814.
- 12 Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, Mokhtarani M, Seyfert-Margolis V, Asare A, Bateman K, Deniz Y: Omalizumab pre-treatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006;117:134–140.