

Allergen skin tests and free IgE levels during reduction and cessation of omalizumab therapy

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Background: The recombinant humanized anti-IgE antibody omalizumab rapidly reduces serum free IgE concentrations and alleviates allergic airway disease. It is not known whether stopping or reducing the dose of omalizumab maintains adequate suppression of free IgE levels and IgE-mediated mast cell activation.

Objective: To determine the effects of omalizumab on serum free IgE and immediate allergen skin test reactivity during initial therapy followed by treatment reduction and cessation.

Methods: Forty patients with perennial allergic rhinitis were randomized to receive 0.015 or 0.030 mg/kg/IU/mL open-label intravenous omalizumab every 2 weeks for 28 weeks, followed by 0.0015 or 0.0050 mg/kg/IU/mL every 2 weeks for 18 weeks. Serum free IgE levels were measured and titrated dust mite allergen skin tests conducted throughout.

Results: At day 98, serum free IgE concentrations were decreased by 96% to 99%, and wheal-and-flare reactions to skin tests were markedly suppressed. After reduced omalizumab doses (day 322), serum free IgE and allergen skin test reactivity increased significantly. On complete discontinuation of therapy (day 378), serum free IgE levels and skin test reactivity returned to baseline levels. Patients with lower initial levels of IgE had significantly less suppression of skin test reactivity.

Conclusion: Omalizumab reduced serum free IgE and immediate skin test reactivity to allergen during initial, high-dose administration. These effects were not fully maintained during dose reduction and returned to baseline after cessation of chronic treatment. (*J Allergy Clin Immunol* 2008;121:506-11.)

Key words: Omalizumab, anti-IgE, IgE, allergic rhinitis, allergen skin tests

Abbreviation used
SPT: Skin prick test

Omalizumab, a humanized monoclonal anti-IgE antibody, represents a form of treatment for patients with chronic allergic airway disease.¹⁻⁵ Early experience with omalizumab suggested that effective suppression of free serum IgE (<10 IU/mL) was associated with the greatest degree of improvement in clinical outcomes.^{4,6-8} Although reductions in serum free IgE occur rapidly and are maintained during long-term administration of omalizumab,^{9,10} it is uncertain whether this effect can be maintained after reductions in the dose or complete discontinuation of the medication. Further, it is not known whether the magnitude of the initial dose of omalizumab significantly influences long-term effects of therapy. Finally, it is uncertain whether the initial concentration of total IgE is related to initial biologic effects of omalizumab or the probability that the dose of the drug may be reduced after prolonged treatment.

Previous research has shown that discontinuation of omalizumab in atopic subjects leads to a rise in free serum IgE levels and a repopulation of the basophil surface with both IgE and FcεR1α receptors.¹¹ In the current study, we investigated the effects of omalizumab on serum free IgE levels and allergen skin test reactivity during steady-state administration of high doses (2-fold to 4-fold higher than currently indicated for clinical use) and variable reductions in drug doses, and after therapy was completely discontinued, in subjects with a broad range of total IgE concentrations.

METHODS

Subjects

Male and female subjects 18 to 65 years of age with histories of mild perennial allergic rhinitis for 2 or more years were eligible for enrollment in the study. At the screening visit, all patients were required to have a serum IgE concentration between 85 IU/mL and 550 IU/mL, a positive skin prick test (SPT) to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* (wheal size >5 mm above saline control), and body weight between 70% and 130% of predicted on the basis of sex and height. Patients were excluded from the study if they were pregnant or lactating; had clinically significant renal, hepatic, or hematologic abnormalities; were receiving allergy immunotherapy; were receiving an intranasal, inhaled, or systemic corticosteroid; and/or had received a mAb preparation during the past year.

The protocol was approved by the institutional review boards for all respective centers, and all subjects provided written informed consent.

Study design

The study was performed as a randomized, open-label, 3-center study (Los Angeles, Calif; Seattle, Wash; and Baltimore, Md). Subjects were divided into 2 groups according to their baseline total serum IgE concentration: low IgE

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was defined as 85 IU/mL to 250 IU/mL, and high IgE was defined as 251 IU/mL to 550 IU/mL. Within each stratification group, subjects were randomized to receive omalizumab 0.015 mg/kg/IU/mL or 0.030 mg/kg/IU/mL intravenously every 2 weeks for 26 weeks (period 1). On the basis of this stratification, there were 4 initial treatment groups: (1) low baseline IgE and low omalizumab dose (0.015 mg/kg/IU/mL); (2) low baseline IgE and high omalizumab dose (0.030 mg/kg/IU/mL); (3) high baseline IgE and low omalizumab dose (0.015 mg/kg/IU/mL); and (4) high baseline IgE and high omalizumab dose (0.030 mg/kg/IU/mL).

After the initial 26-week period of treatment, subjects within each original stratification group were rerandomized for dose reduction to 2 new doses, 0.0050 mg/kg/IU/mL and 0.0015 mg/kg/IU/mL, which they received for 20 more weeks (period 2). The new drug assignment in period 2 resulted in 4 treatment groups: (1) 0.015 mg/kg/IU/mL dose reduced to 0.0050 mg/kg/IU/mL (3-fold reduction); (2) 0.015 mg/kg/IU/mL dose reduced to 0.0015 mg/kg/IU/mL (10-fold reduction); (3) 0.030 mg/kg/IU/mL dose reduced to 0.0050 mg/kg/IU/mL (6-fold reduction); and (4) 0.030 mg/kg/IU/mL dose reduced to 0.0015 mg/kg/IU/mL (20-fold reduction). After discontinuation of treatment, subjects continued to be evaluated for an additional 8 weeks (period 3), ending study participation after a total of 378 days.

Serum total and free IgE concentrations were measured at baseline and every 2 weeks throughout the study. Titrated SPTs to allergen were performed at baseline, middle, and end of treatment period 1 (days 98 and 182), at the end of period 2 (day 322), and at the middle and end of period 3 (days 350 and 378).

Serum IgE and antiomalizumab antibodies

Serum concentrations of total and free IgE were measured by ELISA with the use of an Fc-receptor-IgG chimeric antibody and monoclonal anti-IgE.¹² The lower limits of sensitivity for this assay were 0.32 IU/mL for free IgE and 0.49 IU/mL for total IgE. Serum samples were also screened for the presence of antiomalizumab antibodies by using an ELISA assay, as described previously.¹³

Allergy SPTs

Titrated SPTs were performed to extracts of *D farinae* or *D pteronyssinus* at the time points described. Skin tests consisted of the stock extract (10,000 allergen units/mL; ALK-Abelló, Hørsholm, Denmark) and six 2-fold dilutions (5000, 2500, 1250, 625, 300, and 150 allergen units/mL), each performed in duplicate by using a sterile lancet. Wheal-and-flare reactions were outlined and transferred by tape to a permanent record, allowing for computerized calculation of areas by digital planimetry. Skin test reactivity was quantified by mean wheal-and-flare areas (for the 2 tests at each concentration), summed over the entire dilution series.

Safety and tolerability

Patients underwent clinical evaluations, including history, physical examination, and laboratory testing (blood chemistry, complete blood count and differential, urinalysis, complement components C3 and C4, and antiomalizumab antibodies) every 2 weeks throughout the study.

Statistical analysis

Serum free IgE and total IgE levels were calculated at baseline, over the plateau interval of periods 1 and 2, and at the last measured time point in period 3. Change from baseline in skin reactivity by treatment group was assessed by the Wilcoxon signed-rank test.

RESULTS

Subject characteristics and discontinuations

Demographic and baseline characteristics were well balanced across treatment groups (Table I). Overall, the mean age was 31 years (range, 19-55 years), and 55% of the subjects were male. Baseline IgE levels ranged between 85 IU/mL and 234 IU/mL in the low IgE group, and 253 IU/mL and 523 IU/mL in the high IgE group. Although all patients

TABLE I. Summary of demographic and baseline characteristics by initial treatment group

	Dose (mg/kg/IgE IU/mL)/group			
	0.015/Low IgE	0.015/High IgE	0.030/Low IgE	0.030/High IgE
No.	15	8	16	8
Mean (SD) age (y)	29 (6)	32 (13)	33 (7)	31 (10)
Male sex, %	80	50	50	25
Mean weight, kg (SD)	84 (13)	74 (14)	74 (12)	70 (11)
Baseline IgE, IU/mL				
Mean (SD)	163 (48)	342 (74)	158 (37)	346 (83)
Range	85-234	253-431	88-217	269-523
Other atopic disorders, %				
Allergic asthma	47	75	38	50
Allergic dermatitis	27	13	25	38
Documented food allergy	20	13	19	0
Urticaria	0	13	19	25
Positive skin test history, %				
Ragweed	33	13	50	38
Molds	40	75	81	50
Dust mites	80	88	94	100
Danders	60	63	63	63
Other pollens	53	75	75	75

participating in the study had perennial allergic rhinitis, a large number had other atopic disorders including allergic asthma (49%), atopic dermatitis (26%), documented food allergy (15%), and urticaria (13%). Most patients had a history of skin test sensitivity to dust mites (89%) and a variety of other allergens including molds (62%), animal danders (62%), ragweed (36%), and other pollens (68%).

Two subjects discontinued omalizumab during period 1 of the study: the first subject was in the high IgE group (0.015 mg/kg/IU/mL) and discontinued from the study after 2 doses because of recurrent episodes of urticaria, whereas the second subject, also in the high IgE group (0.030 mg/kg/IU/mL), discontinued omalizumab after 10 doses because of geographic relocation. Four subjects discontinued omalizumab during period 2 of the study: the first subject was in the high IgE group (0.030/0.0015 mg/kg/IU/mL) and was lost to follow-up after receiving 19 doses; the second was in the high IgE group (0.030/0.0050 mg/kg/IU/mL) and discontinued the study after 21 doses because of relocation; the third subject was in the low IgE group (0.030/0.0050 mg/kg/IU/mL) and discontinued omalizumab after 21 doses because of pregnancy; and the fourth, in the high IgE group (0.030/0.0050 mg/kg/IU/mL), discontinued the study after 24 doses because of relocation.

Serum IgE concentrations

All subjects showed substantial reductions from baseline in free serum IgE (>89%) during the plateau phase of period 1 (30-60 days; Table II). All but 3 subjects achieved levels of free serum IgE <10 IU/mL. These 3 subjects belonged to the low baseline IgE group and were receiving the low dose (0.015 mg/kg/IgE IU/mL). Overall, subjects in the high IgE group demonstrated significantly greater reductions in free serum IgE compared with those in the low IgE group, regardless of whether they received the high or low dose of omalizumab ($P < .0001$; Table II).

TABLE II. Concentrations of free IgE

Dose (mg/kg/IU/mL)	Baseline IgE group	No.	Baseline	End of period 1 (day 182)
			Total (free) IgE IU/mL $\pm$ SD	Free IgE IU/mL $\pm$ SD (% reduction)
0.015	High	7	319.1 $\pm$ 71.2	3.3 $\pm$ 1.1 (99.0 $\pm$ 0.35)
	Low	15	153.1 $\pm$ 46.8	5.4 $\pm$ 2.4 (96.0 $\pm$ 2.10)
0.030	High	7	344.4 $\pm$ 81.2	2.1 $\pm$ 0.9 (99.0 $\pm$ 0.32)
	Low	16	150.7 $\pm$ 36.4	2.5 $\pm$ 1.6 (98.0 $\pm$ 1.20)

All IgE values are geometric means. Percent reduction is reported versus baseline.

TABLE III. IgE concentrations at end of periods 1 and 2 (by dosing group)

Treatment group (dose)*	No.	Baseline	End of period 1 (day 182)	End of period 2 (day 322)
		Total (free) IgE IU/mL $\pm$ SD	Free IgE IU/mL $\pm$ SD	Free IgE IU/mL $\pm$ SD (% reduction)
0.015/0.0015	12	230.4 $\pm$ 94.9	3.9 $\pm$ 1.4	13.3 $\pm$ 3.9 (93.0 $\pm$ 3.1)
0.015/0.0050	10	156.8 $\pm$ 84.5	5.8 $\pm$ 2.7	8.6 $\pm$ 3.9 (93.0 $\pm$ 4.4)
0.030/0.0015	9	184.8 $\pm$ 140.0	2.2 $\pm$ 1.0	10.3 $\pm$ 5.7 (93.0 $\pm$ 3.9)
0.030/0.0050	10	181.3 $\pm$ 71.6	2.5 $\pm$ 1.9	5.6 $\pm$ 2.7 (97.0 $\pm$ 2.1)

All IgE values are geometric means. Percent reduction is reported versus baseline.

*Group-initial dose of omalizumab in mg/kg/IU/mL (0.015 or 0.030)/reduced dose of omalizumab in mg/kg/IU/mL (0.015 or 0.0050).

TABLE IV. IgE concentrations at ends of each period (by dosing group)

Treatment group (dose)*	No.	Baseline	Period 1	Period 2	Period 3
		Total IgE IU/mL $\pm$ SD	Free IgE IU/mL $\pm$ SD	Free IgE IU/mL $\pm$ SD	Free IgE IU/mL $\pm$ SD (% reduction)
0.015/0.0015	7	256.7 $\pm$ 78.4	3.5 $\pm$ 1.1	12.7 $\pm$ 4.8	140.2 $\pm$ 65.8 (45)
0.015/0.0050	3	172.4 $\pm$ 113.6	5.7 $\pm$ 5.1	9.0 $\pm$ 7.0	114.0 $\pm$ 19.9 (34)
0.030/0.0015	2	443.0 $\pm$ 93.9	1.4 $\pm$ 1.4	7.2 $\pm$ 10.7	90.3 $\pm$ 201.8 (80)
0.030/0.0050	5	234.3 $\pm$ 65.6	2.3 $\pm$ 1.0	5.1 $\pm$ 2.5	190.1 $\pm$ 101.2 (13)

All IgE levels are geometric means. Percent reduction is reported versus baseline.

*Group-initial dose of omalizumab in mg/kg/IU/mL (0.015 or 0.030)/reduced dose of omalizumab in mg/kg/IU/mL (0.015 or 0.0050).

TABLE V. Allergen skin test reactivity during period 1*

Group	No.	Baseline mm ² $\pm$ SD	Day 98 mm ² $\pm$ SD	Day 182 mm ² $\pm$ SD
0.015 low IgE	15	134 $\pm$ 115	62 $\pm$ 57†	82 $\pm$ 73
0.015 high IgE	7	183 $\pm$ 186	25 $\pm$ 33‡	22 $\pm$ 30‡
0.030 low IgE	16	199 $\pm$ 241	44 $\pm$ 42§	48 $\pm$ 56†
0.030 high IgE	7	140 $\pm$ 98	24 $\pm$ 56‡	1 $\pm$ 3‡

*Mean sum of wheals from entire titration (six 2-fold dilutions) series.

P values are from Wilcoxon signed-rank test (†P = .002; ‡P = .016; §P = .003).

After reduction of omalizumab doses during period 2, serum free IgE concentrations increased in all dose groups (Table III). Only the two 0.0050 mg/kg/IU/mL dose groups maintained mean serum free IgE levels of <10 IU/mL, regardless of whether the doses received in period 1 were high (0.030 mg/kg/IU/mL) or low (0.015 mg/kg/IU/mL). Therefore, the preceding 26-week exposure to higher doses of omalizumab did not reduce the dose required to maintain free IgE suppression below 10 IU/mL during period 2. After the cessation of therapy (period 3), serum free IgE levels could be accurately measured in only 17 of the 45 subjects who started the study (Table IV). The free IgE assay is calibrated over a range of IgE with an upper level (150 ng/mL), above which the assay is inaccurate; the remaining 28 patients had free IgE levels above this limit. In the 17 patients with accurate measurements (who were distributed between the 4 treatment groups), the concentrations of free IgE had increased

substantially, with the exception of the 0.030/0.0015 treatment group; free IgE ranged between 20% and 47% of baseline values.

Titrated allergen SPT

Reactivity to titrated allergy SPTs, as assessed by the sum of wheal areas of the entire allergen dilution series, decreased substantially during period 1 (Table V). The median (interquartile range) percent reduction in the sum of the areas among all subjects for all 4 groups of subjects (pooled analysis) was 84% (27% to 98%) and 86% (43% to 100%) at day 98 and day 182, respectively. On day 322, skin test reactivity increased significantly in all groups with the exception of the 0.030/0.0050 group (Fig 1). In this group (which received the highest doses in both periods 1 and 2), skin test suppression remained intact until omalizumab was completely discontinued. At the end of period 3 (day 378), skin test reactivity in all groups had returned to pre-study baseline levels. Similar changes were observed in the sum of erythema areas across all dose groups at each time point (data not shown).

Relationship between free IgE and skin test suppression

Although most subjects had profound reductions in serum free IgE during period 1 of the study, suppression of allergen-induced wheal areas was variable between subjects. The omalizumab-related effect on wheal areas did not correlate significantly with

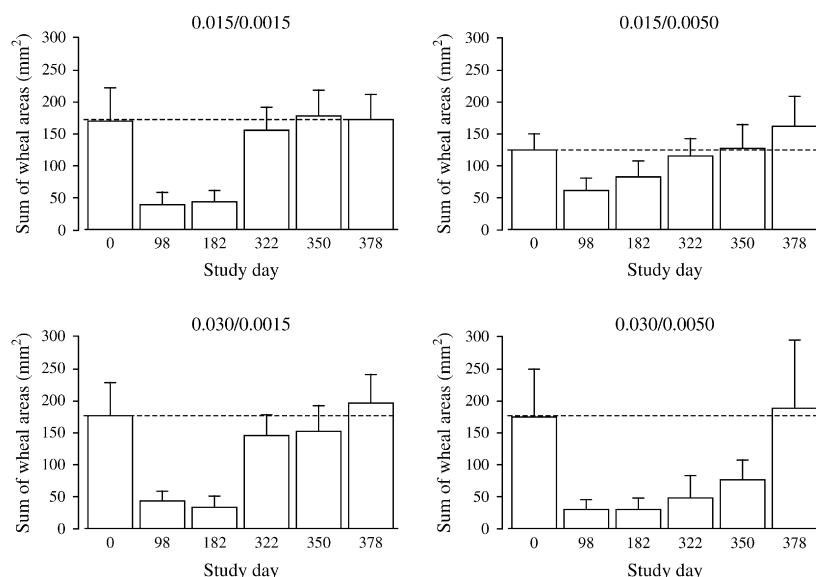


FIG 1. Mean sum of wheal areas by treatment group.

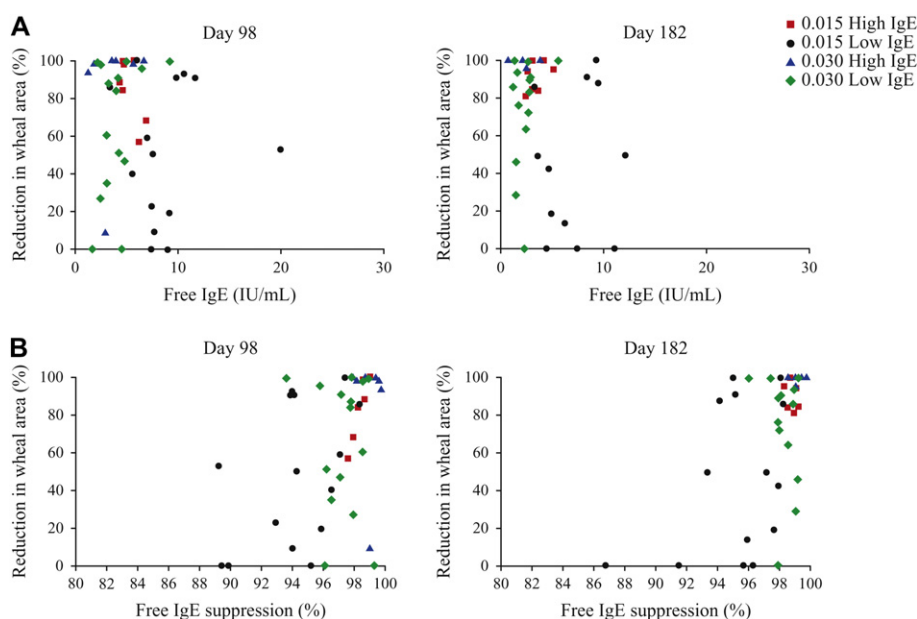


FIG 2. Relationship between free IgE concentrations (A) and change in concentration of free IgE (B), with change in skin test wheal area at days 98 and 182.

either the concentration of serum free IgE (Fig 2, A) or the change in concentration of serum free IgE at days 98 and 182 (Fig 2, B). Patients with low baseline concentrations of serum free IgE had significantly higher levels of serum free IgE and significantly less suppression of skin test reactivity at days 98 and 182.

Safety and tolerability

The most common adverse events overall (regardless of possible relationship to treatment) were infection (primarily upper respiratory infection, which occurred in 60% of subjects in all treatment groups combined), headache (49%), pain (32%), pharyngitis (32%), and back pain (28%). Adverse events were

generally mild or moderate in severity, and the majority of adverse events were judged unrelated to treatment.

Adverse events possibly or probably related to the study drug and occurring in >5% of patients were headache (15%), dizziness (9%), and acute urticaria (9%). Acute urticaria occurred in 4 subjects after the initial omalizumab dose; 3 were in the low-dose group and 1 was in the high-dose group. All 4 subjects were redosed and 2 of these subjects had mild-to-moderate urticarial reactions after redosing. In subjects with acute urticaria, there were no increases observed in plasma histamine or tryptase concentrations, or changes in complement levels. In addition, there were no antibodies detected either to omalizumab or to the

human high-affinity IgE receptor, and epicutaneous skin testing to full-strength omalizumab (5 mg/mL) was negative.

DISCUSSION

In this study we examined whether omalizumab doses can be reduced during long-term treatment while maintaining suppression of serum free IgE, and more importantly, IgE-mediated mast cell activation. Despite the administration of high intravenous doses of omalizumab during the first 28 weeks of the study, both serum free IgE concentrations and skin test reactivity regressed toward baseline during the dose-reduction period and returned to baseline levels after discontinuation of treatment.

These results indicate that circulating free IgE must be reduced to extremely low levels to prevent cutaneous mast cell activation. This concept is supported by *in vitro* data demonstrating that cross-linkage of only a few hundred IgE molecules, or approximately 1% of the approximately 250,000 high-affinity IgE receptors present on a single basophil, is sufficient for cellular activation.¹⁴ Although omalizumab has been demonstrated effectively to reduce circulating free IgE, and hence cell-bound IgE, below this critical threshold, this study shows that even a modest increase in IgE restores the ability of skin mast cells to respond to allergen. Similar data have been generated in *ex vivo* experiments by Saini et al^{11,15} examining allergen-induced histamine release from peripheral blood basophils.

The initial doses of omalizumab given in period 1 of the study were 2-fold to 4-fold higher than those used in pivotal clinical trials in asthma or in current clinical practice, and were administered in this study by the intravenous route. The high doses were selected to ensure maximal reductions in circulating free IgE, allowing for development of pharmacokinetic and pharmacodynamic models with omalizumab. Although both the drug quantity and mode of delivery differ from current dosing guidelines, the fundamental findings from the study remain relevant and applicable to the clinical use of omalizumab.

In addition to these study design issues, our trial was conducted in an open-label fashion without a placebo group. Despite the absence of blinding or a placebo comparator group, the study endpoints were objectively assessed using highly precise methods. Interventional trials using allergy skin testing as an endpoint have demonstrated a minimal placebo effect and highly stable and reproducible results over time.¹⁶ We are therefore confident that the changes observed in skin test reactivity are meaningful and relevant to alterations in mast cell biology.

Few previous studies have evaluated the effects of anti-IgE therapy on allergy skin test responses. Ong et al¹⁷ reported that omalizumab given at the currently approved dose (0.016 mg/kg/IgE IU/mL/mo) significantly reduced both the early-phase and late-phase reactions to intradermal allergen challenge during the eighth week of omalizumab treatment. However, at 98 days, the median reduction in the early skin test response was 24%, which was substantially less than what was observed in our study. The differences in results between these 2 studies may in part be explained by the larger dose of omalizumab used in our study. In addition, Ong et al¹⁷ used the intradermal testing technique and gave large doses of allergen to ensure the development of late cutaneous responses. The quantities of allergen used in that study would likely generate immediate skin test responses on the flat portion of the dose-response curve, making it more difficult to detect reductions in reactivity during treatment with anti-IgE.¹⁷

An interesting observation in our study is that subjects with lower baseline IgE concentrations exhibited consistently less reduction of serum free IgE and skin test suppression than subjects with high levels of baseline IgE. Our findings may be explained by the results of Johansson et al,¹⁸ who noted that in patients with low serum IgE levels (30-74 kU/L), IgE antibodies to specific allergens (eg, cat and house dust mite) made up a much higher fraction of total IgE. In those patients, a mathematical model predicted that despite suppression of serum IgE to 10 kU/L or below, approximately $\frac{1}{4}$ would have high enough concentrations of specific IgE to initiate an allergic reaction.¹⁸ These data, along with our own, have important clinical implications and indicate the need for further study of omalizumab dosing in patients with relatively low levels of serum IgE.

Adverse effects of omalizumab included 4 subjects with acute urticaria after administration of study drug. During this study, all laboratory investigations were negative, suggesting that these events were not a result of IgE-mediated mast cell or complement activation. The cause of these types of reactions to omalizumab has yet to be fully elucidated.

The current study indicates that reduction of omalizumab doses leads to relatively prompt increases in serum free IgE and IgE-mediated mast cell activation. The ultimate relevance of these findings to medical practice will require future trials that monitor asthma symptoms during tapering of omalizumab doses.

It is with regret that we note that Dr Gail Shapiro passed away in August 2006. We acknowledge the importance of her work during the development and performance of this study, because Dr Shapiro's commitment and enthusiasm were key to the completion and success of this project.

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Clinical implications: Six-month to 12-month courses of therapy with omalizumab administered to patients with asthma are unlikely to cause persistent changes in IgE-mediated disease activity.

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