

BIOMARKERS

Changes in Total IgE Plasma Concentration Measured at the Third Month during Anti-IgE Treatment Predict Future Exacerbation Rates in Difficult-to-Treat Atopic Asthma: A Pilot Study

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In severe, difficult-to-treat atopic asthma with sensitization to perennial allergens, monoclonal antibodies directed against immunoglobulin E (IgE) are recognized to be clinically effective. Omalizumab, a recombinant monoclonal antibody, selectively binds to the high-affinity C-epsilon 3 site of human IgE and inhibits the inflammatory cascade in response to antigenic stimuli. Currently, no indicator is available for predicting patients' responsiveness to long-term omalizumab treatment. This study aims to assess the relationship between early changes in plasma IgE concentration and major outcome variables over a 12-month course of omalizumab. **Methods.** Twenty-three nonsmoking, severe asthmatics (14 females; mean age 47.3 years \pm 12.0 SD; mean BMI 25.8 kg/m² \pm 9.6 SD) sensitized to perennial allergens and unresponsive to high doses of common therapies were evaluated during a 12-month period of omalizumab treatment. Variables included total IgE plasma concentrations, Forced Expiratory Volume 1 second (FEV₁) symptom complaints (Asthma Control Test (ACT) score), number of emergency visits, hospitalizations, and exacerbations. The Wilcoxon signed-rank test was used to compare changes observed after the 1-year omalizumab treatment versus baseline. Statistical modelization was used to determine possible relationships between changes in outcomes after 12 months and early changes in plasma IgE (after 3 months of treatment). **Results.** The number of emergency visits, hospitalizations, and exacerbations decreased ($p < .004$, $p < .001$, and $p < .001$, respectively) over the 12-months. In contrast, FEV₁ and ACT score substantially increased (both $p < .001$); the ACT score reaching maximum after only 3 months. The S model showed the best fit and proved the strict relationship between the increase in IgE after 3 months and the exacerbation rate over the 1-year survey (threshold value of ≥ 250 IU/ml, $p < .001$). The improvement in FEV₁ was independent of the increase in IgE. **Conclusions.** When confirmed on a larger population, early changes in IgE may be used as a predictor of future responders to omalizumab in terms of exacerbation rate, thus minimizing the economic burden of anti-IgE therapy.

Keywords anti-IgE, difficult-to-treat atopic asthma, omalizumab, perennial allergens, predictive model, severe bronchial asthma

INTRODUCTION

Asthma is a chronic inflammatory disease which is still highly prevalent, with an estimated 300 million patients (1) affected by this disease worldwide. In Italy, the prevalence of this disease is estimated as 7% for the general population (2). In contrast to the vast majority of cases which respond effectively to inhaled (ICS) (or systemic) corticosteroids (CS) and/or bronchodilators, asthma does not respond satisfactorily to normal therapeutic regimes in 5–10% of patients, even when drugs are administered appropriately and at their highest doses (3).

In severe, difficult-to-treat atopic asthma with sensitization to perennial allergens, monoclonal antibodies directed against immunoglobulin E (IgE) have shown to be clinically effective (4).

Omalizumab is a recombinant monoclonal antibody which selectively binds to the high-affinity C-epsilon 3 site of human IgE. This drug mechanism prevents IgE from binding to mast cells and other effector cells, thus

leading to the inhibition of the inflammatory cascade in response to antigenic stimuli.

Several studies performed on patients with moderate-to-severe allergic asthma have shown the clinical efficacy of anti-IgE treatment in addition to standard therapy (ICS + long-acting beta agonists; LABA) and demonstrated a significant reduction in annual exacerbation rates and severity of respiratory symptoms, together with an increase in FEV₁ values and quality-of-life scores (5–12).

In general terms, the efficacy of omalizumab has been demonstrated in children, adolescents, and adults for doses able to guarantee at least 0.016 mg/kg/IU/ml of IgE for a minimum of 4 weeks (13).

Due to the binding of the monoclonal antibody to human IgE, plasma concentrations of total IgE usually tend to increase progressively during omalizumab treatment. However, this increase does not occur to the same extent in all asthma patients, this variability likely being dependent on their response to anti-IgE treatment in terms of circulating free IgE.

At present no indicator is available for predicting patient responsiveness to prolonged omalizumab treatment, in terms of both lung function and major clinical outcomes.

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The aim of this study was to examine the presence of a possible relationship between early changes in plasma IgE concentration and variation in major clinical outcomes over the 1 year of omalizumab treatment.

MATERIALS AND METHODS

Twenty-three nonsmoking severe atopic asthmatics (14 females; mean age 47.3 years \pm 12.0 SD; range 29–69 years; mean BMI 25.8 kg/m² \pm 9.6 SD) sensitized to perennial allergens and unresponsive to high doses of respiratory drugs (such as daily long acting bronchodilators agents (LABA) + inhaled corticosteroids (ICS) and leukotrienes (LTs) antagonists, slow acting bronchodilators agents (SABA) prn, and frequent courses of oral CS) were evaluated every month over a 12-month period of omalizumab treatment (dose range 150–450 mg). The following variables were monitored: total IgE plasma concentration, FEV₁, symptom complaints by means of the ACT score (14, 15), and number of emergency visits, hospitalizations, and exacerbations. Exacerbations were defined as events of asthma impairment requiring a substantial implementation of regular daily treatment (mainly with systemic steroids) or leading to hospitalization.

Total plasma IgE concentration was measured by means of a solid phase, chemiluminescent immunometric assay (Immulite[®] System, Diagnostic Product Corp., Los Angeles, CA, USA) and expressed in IU/ml.

Lung function was assessed by a spirometric test (Masterscreen, Vyasis-Jaeger, Hoechberg, Germany) and performed after a 24 h wash-out period from any respiratory drug. FEV₁ was expressed as % predicted (Comunità Europea Carbone Acciaio (CECA) 1993, in the range 18–70 years) (16).

Procedures adopted for omalizumab prescription, administration, and monitoring were in strict agreement with guidelines according to the National Ministry of Health (17). This study was approved by the local Ethical Committee (prot. n.1489, approved on 19 January 2010).

Descriptive Statistics

The Wilcoxon signed-rank test was used to compare changes observed for each variable after 12 months of omalizumab treatment versus baseline since it was regarded as the most reliable test for nonparametric comparisons between dependent variables without Gaussian

distribution (verified by the Shapiro–Wilk test); $p < .05$ was considered statistically significant.

Statistical Modelization

Potential relationships existing between changes in IgE and the main long-term clinical outcomes (such as FEV₁, the ACT score, and number of exacerbations, emergency or unscheduled visits, and hospitalizations) were assessed by testing several statistical models.

Our aim was to determine the best statistical model that was capable of effectively describing the potential relationship between changes in long-term outcomes (after a 12-month course of omalizumab), the dependent variable (Y), and early changes in total plasma IgE concentration (measured after the first 3 months of omalizumab treatment), the independent variable (X).

Of the models used (such as linear, logarithmic, inverse, quadratic, cubic, S, compound, power, growth, exponential), the most fitting one was found to be the S model (18):

$$y = e^{b_0 + \frac{b_1}{x}}$$

Differences measured from baseline (t_0) plasma IgE concentration (or FEV₁) after 3 months of treatment (t_{3m}) (variable X) are related to corresponding changes in long-term outcomes (such as FEV₁, the ACT score, and number of emergency visits, hospitalizations, and exacerbations over the 12 months) (variable Y) and described by the formula reported above. Since parameters b_0 and b_1 of the S model are unknown, their values were estimated from data measured from patient samples. The significance level was fixed at 5%.

Statistical analysis was performed using SPSS software version 18 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient demographic characteristics and outcome measures during the anti-IgE treatment period are reported in Table 1. Statistical differences between t_0 and t_{12} are also shown.

All variables were shown to be significantly improved after the 12-month course of omalizumab (Table 1). Moreover, the number of emergency visits, hospitalizations, and exacerbations dropped substantially after

TABLE 1.—Patient clinical and demographic characteristics.

	t_0	t_1	t_2	t_3	t_{12}	P -value
IgE (IU/ml)	246.7 \pm 180.5	385.2 \pm 312.0	606.4 \pm 495.6	598.1 \pm 521.9	601.4 \pm 557.2	
Δ IgE (IU/ml)	–	+138.5 \pm 166.4	+359.7 \pm 369.2	+351.5 \pm 408.6	359.6 \pm 411.4	
FEV ₁ (% predicted)	57.1 \pm 14.4			78.3 \pm 19.9	77.1 \pm 25.0	.001
ACT score	11.9 \pm 3.1			19.1 \pm 4.3	20.3 \pm 4.3	.001
Visits (n)	0.6 \pm 0.8				0.0 \pm 0.0	.004
Hospitalizations (n)	0.9 \pm 0.6				0.0 \pm 0.0	.001
Exacerbations (n)	2.1 \pm 1.1				0.5 \pm 0.7	.001

Note: Data presented as mean values \pm SD at the different experimental times, and p -values of comparisons (t_0 – t_{12}).

1 year of treatment ($p < .004$, $p < .001$, and $p < .001$, respectively), while FEV₁ increased substantially over the same period ($p < .001$). With regard to changes in respiratory signs, the ACT score reached its maximum value (indicating improvement) at the third month of treatment ($p < .001$) and did not show any further significant improvement over the remaining 9 months ($p = .16$) (Table 1).

Trends in all variables were also compared by gender, and no statistical difference was observed.

Modelization

Results of the S model are reported in Table 2. In addition, the report for parameter estimates for b_0 (the constant of the model) and b_1 (the functional coefficient for X) is presented in the final two columns of Table 2.

Only changes in the number of exacerbations and FEV₁ were entered into the modelization, since the number of all other discrete variables was too small.

The peculiar sigmoid shape of the identified function shows that the stabilization of the exacerbation rate can be achieved when the mean variation of total IgE plasma concentration measured at the third month of omalizumab treatment is ≥ 250 IU/ml. Moreover, the model was shown to be highly statistically significant ($p < .001$), with an adjusted square coefficient of 0.525. This implies that only when the variation in total IgE plasma concentration measured at the end of the first 3 months of treatment is ≥ 250 IU/ml, a significant inversion of the exacerbation trend is predictable for the patient (Figure 1).

The same methodological approach was applied to examine the presence of a relationship between changes in IgE concentration after 3 months and FEV₁ variation observed after 1 year of treatment (variable Y).

Data reported in Table 3 indicate that in this case no model was able to identify any significant relationship between X and Y variables, suggesting that variations in FEV₁ are independent of variations in total plasma IgE concentration (Figure 2). Furthermore, the model characterized by the lowest p -value was referred to as the “power model” ($p = .109$), even if the corresponding level of significance was not found to be statistically acceptable and figures obtained discourage any further attempt of modelization.

DISCUSSION

Despite the fact that severe asthma is characterized by a low rate of prevalence, this disease still places a

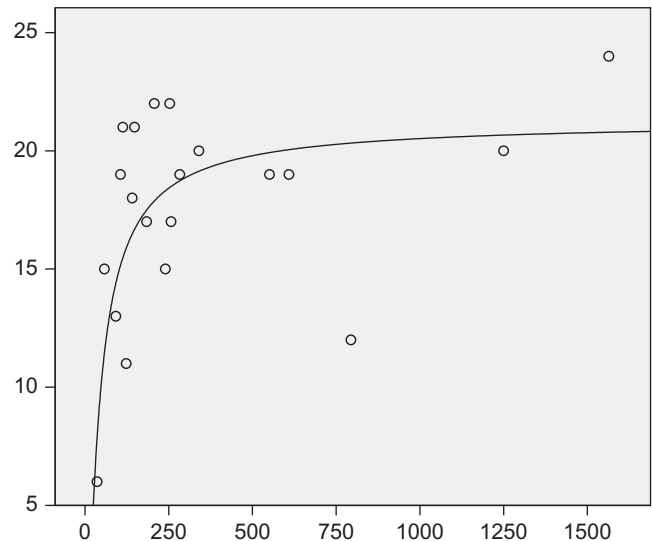


FIGURE 1.—Graphic representation of the relationship identified by the S model between changes in total IgE plasma concentrations obtained after 3 months (X variable) and changes in *n*. exacerbations after 12 months of omalizumab (Y variable).

substantial strain on health-care resources (19). Since a significant proportion of patients suffering from severe asthma still do not receive effective treatment, the interest in developing new therapeutic approaches that are targeted toward the control of severe asthma is constantly increasing. Current research is therefore mainly oriented toward the optimization of long-term clinical and economic outcomes in difficult-to-treat asthma.

The biologic treatment of severe persistent atopic asthma that is uncontrolled with usual highly dosed respiratory drugs has been in clinical use since 2006. omalizumab is a humanized monoclonal antibody that selectively binds to the high-affinity C-epsilon 3 site of human IgEs, thus blocking the cascade of biological events leading to the pronounced clinical expression of bronchial asthma (12, 20, 21).

Several studies carried out on severe atopic asthmatics sensitized to perennial allergens have clearly demonstrated the efficacy of omalizumab in terms of a significant reduction in the frequency of moderate-to-severe exacerbations, emergency visits, hospitalization rate, use or systemic steroids, and respiratory symptoms, with an improved quality of life and reduced health-care costs (6–11, 22, 23). Other studies have also shown that omalizumab is extremely well tolerated (24, 25). Moreover, data from a pharmacoeconomic study conducted over a 12-month period that was specifically designed to more closely reflect the real-life setting further

TABLE 2.—Summary of the S model and the parameter estimates.

Equation	Summary of the model					Parameter estimates	
	R ²	F	DF1	DF2	Significance	Constant	b ₁
S	0.525	19.876	1	18	.000	3.057	−35.961

Notes: The dependent variable is “number of exacerbations at the 12th month.” The independent variable is “the change in plasma total IgE concentration measured at the third month.”

TABLE 3.—Summary of all models and the parameter estimates.

Equation	Summary of the model					Parameter estimates			
	R^2	F	DF1	DF2	Significance	Constant	b_1	b_2	b_3
Linear	0.040	0.750	1	18	.398	19.685	0.007		
Logarithmic	0.106	2.145	1	18	.160	-4.978	5.033		
Inverse	0.082	1.606	1	18	.221	26.793	-670.379		
Quadratic	0.220	2.398	2	17	.121	10.273	0.064	-3.82E-005	
Cubic	0.232	1.610	3	16	.226	6.920	0.095	-9.63E-005	2.58E-008
Compound	0.077	1.509	1	18	.235	14.411	1.001		
Power	0.136	2.835	1	18	.109	3.594	0.291		
S	0.078	1.524	1	18	.233	3.080	-33.442		
Growth	0.077	1.509	1	18	.235	2.668	0.001		
Exponential	0.077	1.509	1	18	.235	14.411	0.001		

Notes: The dependent variable is "FEV₁ changes at the 12th month of treatment." The independent variable is "the change in plasma total IgE concentration measured at the third month."

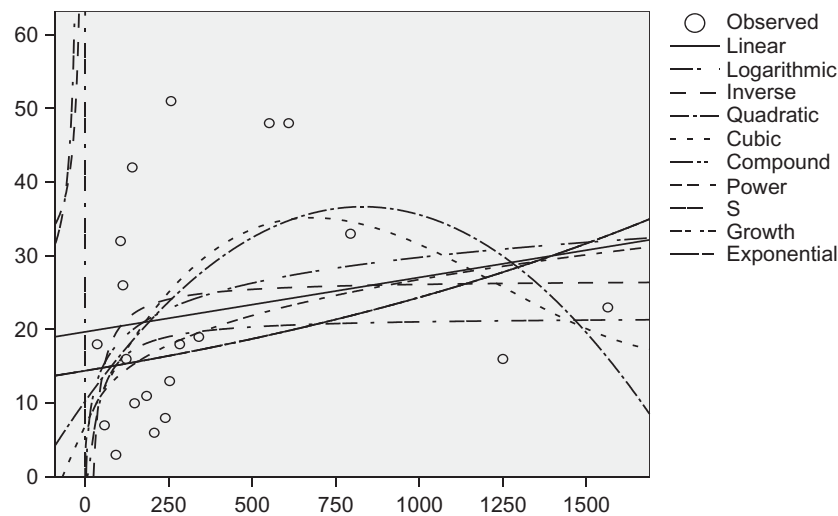


FIGURE 2.—Graphic representation of all models used for investigating any possible relationship between changes in total IgE plasma concentrations after 3 months (X variable) and changes in FEV₁ % prediction after 12 months of omalizumab (Y variable).

confirmed that long-term treatment with omalizumab reduced exacerbations by 59% in uncontrolled severe asthma, previously therapeutically optimized (10).

However, even though clinical (e.g., lung function, quality of life) and economic outcomes definitively confirm the clinical efficacy and the cost-effectiveness of omalizumab treatment, to our knowledge no indicator is currently available that is capable of predicting a patient's response to long-term anti-IgE therapy.

Since anti-IgE therapy can demonstrate variable efficacy in severe uncontrolled asthma, we thought this specific aspect warranted further investigation. As with any biological strategy, initial health-care costs may be incurred (sometimes over several months) before demonstrating therapeutic value in real life (absolute cost-effectiveness in these cases). With this in mind, our clinical and economic interest was focused on generating a predictive algorithm capable of discriminating responders from nonresponders to long-term omalizumab treatment, in the shortest possible time.

Data from this study, besides further confirming the therapeutic value of a 1-year anti-IgE therapeutic approach in real life, have shown that a substantial

clinical response to treatment can be expected in severe uncontrolled asthma patients, when the increase in their total IgE plasma concentration is at least 250 IU/ml after only 3 months of omalizumab therapy.

This finding was found to be highly statistically significant and correlated very tightly with the concomitant drop in exacerbation rate monitored over the 12-month period. In contrast, the change in lung function over the year (i.e., FEV₁) was not associated with an increase in IgE concentration, thus suggesting a clear independence between these two clinical long-term outcomes. As the improvement in FEV₁ reaches its maximum after 3 months of treatment, the consequent clinical implication is that changes in FEV₁ over time do not represent a reliable indicator for evaluating the long-term efficacy of anti-IgE therapy.

Data derived from this study support the hypothesis that the absolute increase in IgE of ≥ 250 IU/ml from baseline after only 3 months of anti-IgE treatment is independent of the original total plasma concentration. This could be used as a sensitive and reliable predictive index of future long-term clinical responsiveness to omalizumab in clinical practice.

The possibility of discriminating responders from nonresponders in only a few weeks, in terms of their future exacerbation rate, also provides the advantage of minimizing the economic impact of anti-IgE administration, which would otherwise have been delivered for several months further, prior to establishing its clinical benefit.

Another clinical implication emerging from these data is that respiratory symptoms (such as ACT score) ameliorate rapidly and significantly over the first few months of treatment in responder patients, without any further significant improvement in the remaining months. This time-course closely paralleled that of the increase in IgE concentration.

CONCLUSIONS

When confirmed on larger samples of patients, this novel predictive index should serve to update the present pharmaco-economic indices which characterize the cost-effectiveness of the anti-IgE therapy (such as the gained Quality Adjusted Life Years (QALY) and the Incremental Cost Effectiveness Ratio (ICER) value). These indices, which are already regarded as quite convenient for a long-term biological treatment (10), would be further optimized and much more closely represent conditions in real life.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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