

Original article

Specific IgE serum concentration is associated with symptom severity in children with seasonal allergic rhinitis

Background: The impact of allergen-specific and total IgE serum levels before and during the pollen season on symptom severity as well as efficacy of treatment with anti-IgE requires further delineation.

Methods: Birch and grass pollen allergic patients aged 6–17 years with seasonal allergic rhinitis (SAR) were analyzed for the association of IgE serum concentration with symptom severity and rescue medication use (combination: symptom load, SL) during the grass pollen season. Reference group A ($n = 53$) received placebo, while group B ($n = 54$) received Omalizumab (anti-IgE) monotherapy before and during the grass pollen season.

Results: Patients on placebo with high baseline specific grass pollen IgE (> 50 kU/l) had a significantly higher SL compared with those with low IgE levels (≤ 50 kU/l): SL 1.28 vs 0.61, $P = 0.015$. This association was nonexistent in patients treated with anti-IgE. In contrast, baseline total IgE levels did not correlate with SL in any group. Patients with anti-IgE treatment and high free total IgE levels (> 16.7 ng/ml) had a significantly higher SL compared with those with low free total IgE levels (≤ 16.7 ng/ml): SL 0.63 vs 0.23, $P = 0.031$.

Conclusions: Baseline specific IgE, but not total IgE, is associated with symptom severity during the pollen season in children with SAR. Likewise, the symptom load in SAR patients with anti-IgE correlates with free total IgE levels. Although further research in larger populations is needed to confirm our findings, our data suggest that specific IgE can be used as a parameter for patient selection for this kind of treatment.

**C. Rolinck-Werninghaus^{1,*}, T. Keil^{2,*},
M. Kopp³, S. Zielen⁴, U. Schauer⁵,
A. von Berg⁶, U. Wahn¹,
E. Hamelmann¹, the Omalizumab
Rhinitis Study Group**

¹Pediatric Pneumology and Immunology; ²Institute for Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Berlin; ³University Children's Hospital, Freiburg; ⁴University Children's Hospital, Frankfurt; ⁵University Children's Hospital, Bochum; ⁶Marien Hospital, Wesel, Germany

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Eckard Hamelmann
Department of Pediatric Pneumology and Immunology
Charité
Augustenburger Platz 1
D-13353 Berlin
Germany

*These authors contributed equally.

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There are rather conflicting results with regard to an association between specific IgE (sIgE) levels and symptoms of seasonal allergic rhinitis (SAR) (1–5) or asthma (6). Most of these data were derived from adult patients undergoing no specific treatment besides the use of rescue medication. In contrast, analyzing preschool children from two birth cohorts, the authors found robust positive association between sIgE levels to various allergens and the prevalence of asthma/current wheeze, allergic rhinitis or atopic eczema (7–9). These data clearly pointed towards a pivotal role of sIgE for the development of allergic diseases in this age group (10), but did not answer the question of an effect on disease severity and outcome.

Conclusive statements regarding the impact of IgE levels on symptom severity of SAR were so far always hampered by the fact that only indirect association

between these two parameters could be drawn. The availability of data from a well powered, placebo-controlled, multi-center study of children and adolescents with SAR treated with the blocking monoclonal anti-IgE antibody (Omalizumab) (11) gave us the unique opportunity to shed new light on this topic, as it allowed us to assess directly the influence of IgE levels on SAR symptoms and treatment efficacy during the specific season.

Considering the mode of action of Omalizumab, clearly it is best to evaluate IgE levels to predict the efficacy of treatment. Previous preclinical (12–14) and clinical studies (15–18) have revealed the crucial role of remaining serum levels of noncomplexed, free total IgE (tIgE) under treatment with anti-IgE in this respect (12–18). Studies on adult SAR patients (19, 20) showed a significant correlation between free tIgE levels and symptom severity and rescue medication scores and suggested that clinical effectiveness was only achieved when serum free tIgE levels were reduced below 25 ng/ml (19, 20).

To elucidate this point further, we investigated in this study whether serum levels of tIgE (within the range

Abbreviations: IgE, immunoglobulin E; r , Spearman rho correlation coefficient; SAR, seasonal allergic rhinitis; sIgE, specific immunoglobulin E; SIT, specific immunotherapy; SL, symptom load; tIgE, total immunoglobulin E.

indicated for adequate treatment) or of allergen-specific sIgE before and during the specific allergen season are associated with either the symptom load (a combination of symptom severity and use of rescue medication) or the efficacy of anti-IgE treatment in children with SAR.

Methods

Patients

Children and adolescents with a clinical history of at least 2 years (median duration 5 years) of birch- and grass-pollen induced SAR aged 6–17 years ($n = 221$) were included in this study. Sensitization against birch- and grass-pollen was confirmed by measurement of specific IgE serum levels (≥ 0.7 U/l; CAP class ≥ 2). Exclusion criteria were a history of perennial allergic rhinitis, serum tIgE levels outside the range 30–1300 IU/ml and a bodyweight of > 100 kg for reasons of dosing the anti-IgE antibody.

All patients were assigned to subcutaneous specific immunotherapy (SIT) with *either* birch pollen (group A + B) *or* grass pollen (group C + D) (ALK-Scherax/Abello, Berlin, Germany). After completion of the SIT titration phase (12 weeks), either placebo (group A + C) or anti-IgE antibody (group B + D, Omalizumab®; Novartis, Nuremberg, Germany) was added 4 weeks before the start of the birch pollen season and continued throughout the grass pollen season. The study was completed by 219 patients (99.1%). The results were retrospectively derived from an intervention study on a combination of specific immunotherapy and anti-IgE treatment [for details of the protocol refer to (11)].

For the present analysis aiming to assess the association of IgE levels with symptom load in patients with or without anti-IgE therapy, study results during the grass pollen season were compared between reference group A (SITbirch + placebo, $n = 53$), which received SIT with an irrelevant allergen, and the intervention group B (SITbirch + anti-IgE, $n = 54$), which additionally received anti-IgE treatment. Analysis of the data during the birch pollen season for the according groups (C vs D, both receiving SITgrass) revealed comparable results (data not shown).

Symptom load

The clinical outcome was analyzed by calculating the symptom load (SL), i.e. the sum of the mean daily symptom severity score plus the mean daily rescue medication score. During the defined local pollen season, patients (or in children not capable enough their parents) recorded daily symptom severity on a four-point scale (0 = none to 3 = severe) for the following three ocular and four nasal symptoms: itchy, watery or red eyes and sneezing, itchy, runny or stuffy nose. For each patient, the daily symptom severity score was defined as the sum of the scores for nasal and ocular symptoms divided by seven. Patients' symptom severity score for the grass pollen season was defined as the arithmetic mean of the daily scores of all days during the season. Patients were provided with the following rescue medication and instructed to use it at standard dosing only to control symptoms, not to be used prophylactically: levocabastine eye drops and nasal spray, inhaled salbutamol, cetirizine tablets and oral prednisolone. The rescue medication intake was assessed on a four-point scale according to the daily maximal score (0, no rhinitis medication; 1, topical nasal, ocular or lung treatment apart from corticosteroids; 2, systemic antihistamines; 3, topical or systemic corticosteroids for nose or lung). For each patient, the daily rescue medication score was defined as the maximum score of the used

rescue medication (0–3). Patients' rescue medication score for the grass pollen season was defined as the arithmetic mean of the daily scores of all days during the season. During the birch pollen season, patients in all groups documented lower symptom severity and rescue medication use when compared with the grass pollen season. This was presumably because of low birch pollen exposure.

Total IgE and specific IgE

Blood samples were drawn at baseline before the pollen seasons and during the closest scheduled visit after beginning of the defined grass pollen season (at 24 weeks) and analyzed for concentrations of tIgE and sIgE antibody titers to birch and grass pollen amongst others. Serum levels of tIgE and sIgE were determined by fluorescence enzyme immuno assay (FEIA) using the Pharmacia CAP-system (Pharmacia Diagnostics, Uppsala, Sweden) (21).

Free total IgE

Free total IgE was analyzed as described elsewhere (22) using a solid phase ELISA on plates coated with human IgE receptor α -chain IgG chimera (Fc ϵ RI-IgG) capturing only free IgE, that is IgE not in a complex with anti-IgE antibodies.

Statistical analysis

For the two study groups included in this study, all analyses were performed on the intention-to-treat population. This was defined as all patients who received at least one dose of drug (Omalizumab) or placebo and for whom an efficacy evaluation (symptom load) was performed. For associations between specific, total or free total serum IgE concentrations and symptom load (aggregated from symptom severity and rescue medication scores as explained above), we calculated nonparametric Spearman's rank correlation coefficients because neither the IgE data nor the symptom load data were normally distributed; furthermore, the symptom load was based on a categorical assessment (see above). To test differences between two groups regarding the symptom load, we used the nonparametric Mann–Whitney *U*-test. A two-sided *P* value < 0.05 was regarded as statistically significant. All analyses were performed using SPSS version 13.0 for Windows (Chicago, Illinois, USA).

Results

Association of specific IgE with symptom load and anti-IgE treatment

In patients without anti-IgE treatment, specific IgE to grass pollen measured *at baseline* showed a weak but statistically significant correlation with the SL *during the grass pollen season* ($r = 0.34$, $P = 0.011$). Patients who had a high baseline sIgE (> 50 kU/l, i.e. CAP-class 5 or 6) had a significantly higher SL during the grass pollen season compared with patients with sIgE levels ≤ 50 kU/l (Table 1).

Specific IgE measured *during the pollen season* in patients without anti-IgE treatment showed a slightly stronger correlation with the seasonal SL compared with the specific IgE measured preseasonally, also statistically significant ($r = 0.36$, $P = 0.011$). As at baseline, patients

Table 1. Association of grass pollen specific immunoglobulin E (at baseline and during season) with symptom load in patients with and without anti-IgE treatment

Specific immunoglobulin E	Patients (n)	Symptom load median (min–max)	P-value
Preseason (baseline)			
Without anti-IgE treatment (median 52.0 kU/l, min–max 1.0–125.0)	54	0.89 (0.02–6.00)	–
≤ 50 kU/l	26	0.61 (0.02–2.34)	0.015
> 50 kU/l	28	1.28 (0.08–6.00)	
With anti-IgE treatment (median 66.3 kU/l, min–max 0.9–125.0)	54	0.49 (0.00–3.59)	–
≤ 50 kU/l	25	0.58 (0.03–3.59)	0.256
> 50 kU/l	29	0.41 (0.00–1.35)	
During season*			
Without anti-IgE treatment (median 54.2 kU/l, min–max 1.4–125.0)	51	0.89 (0.02–6.00)	–
≤ 50 kU/l	25	0.62 (0.02–2.34)	0.019
> 50 kU/l	26	1.35 (0.08–6.00)	

*Seasonal sIgE levels were not assessed in patients treated with anti-IgE because of IgE-anti-IgE complexation.

with a high seasonal sIgE > 50 kU/l had a significantly higher SL during the grass pollen season compared with patients with sIgE levels ≤ 50 kU/l (Table 1).

With complexation of serum IgE from anti-IgE treatment there was no correlation of preseasonal sIgE with seasonal SL ($r = -0.04$, $P = 0.794$; Fig. 1). Accordingly, in patients treated with anti-IgE the subgroup with a high preseasonal sIgE did not differ significantly from those with lower values in respect to SL during grass pollen season (Table 1). Specific IgE levels during the pollen season were not assessed in patients treated with anti-IgE because of IgE-anti-IgE complexation.

Association of total IgE with symptom load and efficacy of anti-IgE treatment

Total IgE serum levels at baseline did not correlate with the SL during the grass pollen season either in patients without anti-IgE treatment ($r = -0.19$, $P = 0.889$) or in those receiving co-seasonal anti-IgE treatment ($r = 0.15$, $P = 0.284$; Table 2).

Total IgE values were classified into categories below or above the median value of the respective group. Because of the complexation of serum IgE with anti-IgE antibodies, median tIgE of the placebo group was used to categorize serum levels measured in anti-IgE treated patients. Irrespective of therapy, we did not find an association between the categorized baseline tIgE serum levels and the SL (Table 2).

Further, tIgE levels measured during the grass pollen season in patients without anti-IgE treatment did not correlate with the SL ($r = 0.17$, $P = 0.215$; Table 2). Patients with high tIgE titers were not more affected by

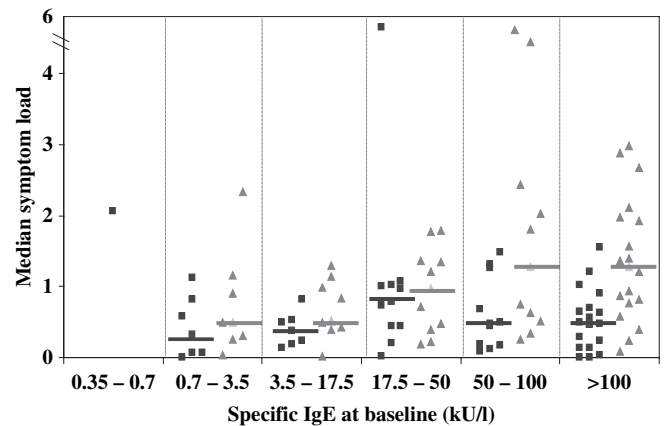


Figure 1. Specific IgE to grass pollen at baseline (categorized in analogy with CAP-classes) is associated with median symptom load during the grass pollen season in patients without (▲; median —, $n = 53$) or with anti-IgE treatment (■; median —, $n = 54$).

seasonal symptoms and treatment with anti-IgE did not change this finding (Table 2).

Association of free total IgE with symptom load and efficacy of anti-IgE treatment

Free tIgE, which is serum tIgE not complexed by binding to anti-IgE antibodies, was measured during the pollen seasons in patients receiving therapy with anti-IgE. Serum levels during the grass pollen season showed a trend for a weak positive correlation with SL during the grass pollen season (median free tIgE_{24 weeks}: 16.7 ng/ml, median SL 0.49, $n = 54$, $r = 0.23$, $P = 0.089$), although patients treated with anti-IgE showed rather few symptoms during the season (data not shown).

When free tIgE serum levels during the grass pollen season were classified into categories below or above median of the respective group, the difference between both with regard to SL became statistically significant: High free tIgE levels were associated with a high SL (Fig. 2).

Discussion

The impact of specific and total IgE serum levels on symptom severity and efficacy of anti-IgE treatment in patients with allergic airway diseases is still a matter of debate. To further delineate these issues, we retrospectively studied data from a multi-center trial in children and adolescents with birch- and grass-pollen associated SAR treated with anti-IgE or placebo, allowing to directly addressing this issue (11).

Specific IgE levels to grass pollen at baseline as well as during the pollen season were associated with seasonal symptoms and use of rescue medication (combined: SL) of patients receiving no anti-IgE treatment. Particularly,

Table 2. Association of total immunoglobulin E (at baseline and during season) with symptom load in patients with and without anti-IgE treatment

Total immunoglobulin E	Patients (n)	Symptom load, median (min–max)	P-value
Preseason (baseline)			
Without anti-IgE treatment (median 291 kU/l, min–max 24–3681)	53	0.89 (0.02–6.00)	–
SL-tIgE above median	26	1.07 (0.02–6.00)	0.450
SL-tIgE below median	27	0.83 (0.03–4.45)	
With anti-IgE treatment (median 331 kU/l, min–max 38–1305)	54	0.49 (0.00–4.65)	
SL-tIgE above median	25	0.50 (0.00–4.65)	0.456
SL-tIgE below median	29	0.46 (0.00–1.31)	
During season*			
Without anti-IgE treatment (median 431 kU/l, min–max 56–4762)	53	0.89 (0.02–6.00)	–
SL-tIgE above median	26	0.90 (0.02–4.45)	0.644
SL-tIgE below median	27	0.91 (0.19–6.00)	

*Seasonal tIgE levels were not assessed in patients treated with anti-IgE because of IgE-anti-IgE complexation.

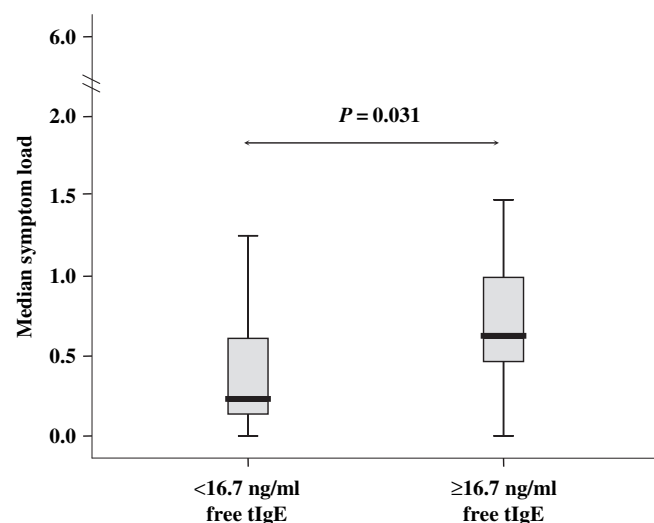


Figure 2. Free total IgE serum levels during the grass pollen season categorized into values below and above the median of untreated patients (16.7 ng/ml) are associated with median seasonal symptom load in patients with anti-IgE treatment ($n = 54$).

a very high preseasonal or seasonal sIgE concentration (sIgE > 50 kU/l) resulted in a significantly higher SL during the grass pollen season. This finding may seem obvious, but is hardly reflected by the published literature: the picture seems rather clear for the development of allergic diseases in young children, where two different European birth cohort studies demonstrated a positive association of sIgE levels against various allergens and the prevalence of asthma/current wheeze, allergic rhinitis

or atopic eczema (7–9). However, the impact of sIgE levels on the severity of symptoms was not assessed in these studies. In contrast, adult patients with SAR have been investigated by several studies in this respect. Some investigators found a positive association between sIgE levels and clinical symptoms (1–3), although symptoms were also dependent on other factors, such as the ease of histamine release by basophils. Other studies did not find strong associations or reported inconsistent findings (4, 5). This inconsistency may be explained by differences in allergens, age or other characteristics of the patient populations studied. At least this seems to be the reason for a marked variability in the outcome of a variety of studies investigating the capacity to predict symptomatic food allergy from sIgE levels in children (23). We therefore assume that some of the above-mentioned differences among studies in respiratory allergies may be explained by the varying parameters of the allergens studied, the age of the patients and the measurements of clinical disease severity.

To our knowledge our present study is the first to demonstrate that treatment with anti-IgE abolished the positive correlation of sIgE serum levels and seasonal symptoms, thus demonstrating the role of sIgE for symptom severity. In the first efficacy study of anti-IgE in SAR patients, Casale et al. (22) reported a weak correlation of ragweed-specific IgE baseline levels and seasonal symptom scores ($r = 0.33$, $P < 0.0001$). However, the study failed to demonstrate a significant improvement in treated subjects because of insufficient dosage of anti-IgE. Therefore, their results should be evaluated with caution and rather interpreted as findings in untreated patients, which then correspond to our own data. Interactions of anti-IgE with local immune responses in the end organs have recently been investigated *in vitro* (24–26). For patients with SAR, Corren et al. (26) demonstrated that anti-IgE significantly reduced both serum and nasal lavage IgE levels, with a corresponding decrease in nasal responses to allergen challenge. This is very well in line with our present data.

Neither for preseasonal nor seasonal tIgE levels (within the range indicated for adequate treatment) we found any association with the severity of SAR symptoms. Not even very high tIgE serum titers were associated with an elevated SL. This, only at first sight, contrasts data from epidemiological studies with evidence for a strong correlation between serum tIgE levels and the prevalence of allergic asthma or airway hyper-responsiveness (27, 28). In a prospective study on preschool children, Custovic et al. (9) found no association of tIgE antibody levels with the probability of current wheeze. Besides these findings, there are little data on the correlation of tIgE levels with clinical symptoms of allergic asthma or rhinitis, and none so far on the impact of anti-IgE treatment. One study investigated persisting postseasonal symptoms of allergic farmers in respect of IgE levels showing positive association between preseasonal tIgE

levels and methacholine reactivity at the end of the season (6). For patients with SAR, two studies on adult patients are in line with our findings, reporting no correlation between tIgE concentrations and seasonal symptom-medication scores (3, 5).

Early clinical studies with anti-IgE implicated that the dose of anti-IgE treatment should be sufficient to suppress free tIgE levels to the lowest possible degree to reach clinical efficacy. Accordingly, post-treatment free tIgE serum concentrations of below 45 ng/ml (22) or below 25 ng/ml (19) have been postulated as required to gain significant treatment effect. Following the recommended dosage scheme that has been established from these data, we observed free tIgE levels below 45 ng/ml in all but one of our patients (52 ng/ml, $n = 1/54$, 2%), and levels below 25 ng/ml in 43 of 54 patients (80%). Although this reduction in free tIgE levels seems very sufficient, we found some degree of correlation between free tIgE serum levels and SL both measured during the respective grass pollen season: patients with high free tIgE values (above median, i.e. 17–52 ng/ml) suffered from significantly more severe symptoms than patients with lower values. This supports data from other studies in patients with SAR reporting a significant correlation of free tIgE levels with symptom severity and rescue medication use (20). In the asthma studies with anti-IgE, unfortunately, the reported free tIgE levels have not been evaluated with respect to symptoms (15–18).

According to our data, tIgE levels were not associated with symptom severity or monitoring of the efficacy of anti-IgE therapy, at least for this type of disease and patient. In contrast, serum sIgE showed a positive association with symptom severity during the pollen season. For patients with SAR, we therefore only partially agree with Hamilton et al. (29), who suggested that accurate monitoring of total and allergen-specific IgE, together with free tIgE levels, may help optimize dosing and maximize the efficacy of anti-IgE therapy. Until easier and more affordable assays for analysis of the only convincing parameter in this context, free specific IgE, are available, we consider free total IgE as the most

meaningful parameter for monitoring of treatment with anti-IgE. However, this assay is not available for a routine estimation, so that other tests concentrating on cellular reactivity, such as fluorescence-activated cell sorter (FACS)-analysis of CD63 up-regulation on peripheral basophils upon *in vitro* allergen stimulation (30), may fill the gap, despite obvious technical drawbacks regarding their application in daily practice.

Treatment with the novel concept of anti-IgE is a very intriguing and promising new strategy for a wide range of allergic patients. Presently, it is, however, limited by a rather narrow label and uncertainties in predicting the most promising patients in terms of treatment efficacy and safety. We agree with the most recent Cochrane analysis on anti-IgE treatment of allergic asthma (31) stating that it is not fully clear from the available literature why some patients respond so well and others do not. At least from our findings in children and adolescents with SAR it seems that patients with high baseline sIgE levels will suffer more severe symptoms without anti-IgE therapy and will clearly benefit better from anti-IgE therapy, without knowing if this is the same for asthmatic patients. In the light of decreasing medical budgets, we consider it mandatory to proceed with further studies that aim to establish clinical or diagnostic parameters helping to define patients that benefit most from this promising form of therapy (32). Further research in larger study populations is now required to confirm our findings and to establish sIgE-based diagnostic 'decision points' – as have been established for food allergy (23) – to predict symptom severity during the relevant season and allow judging the efficacy of anti-IgE treatment.

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