

Original article

Relationship between pretreatment specific IgE and the response to omalizumab therapy

Background: Omalizumab, an anti-IgE antibody, has proven efficacy in patients with moderate-to-severe and severe persistent allergic (IgE-mediated) asthma. While previous analyses have had some limited success in predicting which patients will gain greatest benefit based on pretreatment baseline characteristics, it remains important to try to improve this predictability.

Methods: Following a run-in phase, patients (12–75 years) inadequately controlled despite current therapy were randomized to receive omalizumab or placebo for 28 weeks in a double-blind, parallel-group, multicenter study (INNOVATE). Univariate analyses were performed to assess whether pretreatment specific IgE serum levels and related variables could be identified that were predictive of a response to omalizumab patients ($n = 337$) enrolled in INNOVATE. Response was measured via variables including exacerbations, QoL, FEV₁ and physicians' overall assessment.

Results: A total of 305 patients (90.5%) were sensitive to more than one allergen and the majority of patients were positive to D1 *Dermatophagoides pteronyssinus* and D2 *Dermatophagoides farinae*. Patients with relatively high values of D1 or D2, but with these making a relatively low contribution to total specific IgE load, appeared to attain most benefit from omalizumab. However, no consistent predictive effect for omalizumab response was observed either for total specific IgE or levels of IgEs specific for individual allergens.

Conclusions: Based on these data, pretreatment allergen-specific IgE levels do not provide any better prediction of response to treatment as compared with pretreatment total IgE. At present, the most reliable method of identifying patients who respond to omalizumab treatment remains a physician's assessment.

U. Wahn¹, C. Martin², P. Freeman²,
M. Blogg², P. Jimenez³

¹Charité – Universitätsmedizin Berlin, Berlin, Germany; ²Novartis Horsham Research Centre, Horsham, UK; ³Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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Professor Ulrich Wahn
Charité - Universitätsmedizin Berlin
Augustenburger Platz 1
D-13353 Berlin
Germany

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Asthma is a chronic inflammatory disorder of the airways and has an allergic component in the majority of cases (1, 2). Allergic asthma is characterized by the presence of immunoglobulin E (IgE) antibodies against one or more common environmental allergens such as house dust mite, animal dander and moulds (1, 3–5). The risk of developing asthma increases with increasing levels of serum IgE (6) and a high proportion of patients with asthma of all severities show skin-prick positivity (7–9).

In patients sensitized to a particular allergen, exposure to the allergen leads to the cross-linking of specific IgE bound to high-affinity IgE receptors (FcεRI) on the surface of basophils and mast cells, triggering the release of preformed pro-inflammatory mediators and newly synthesized cytokines and chemokines that trigger and perpetuate airway symptomatology (2, 10).

Omalizumab, an anti-IgE antibody, has demonstrated efficacy in patients with moderate-to-severe and severe persistent allergic (IgE-mediated) asthma (11, 12). In the European Union, omalizumab is indicated for the treat-

ment of severe persistent IgE-mediated allergic asthma that is inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus a long-acting β₂-agonist (LABA). In a 28 week, randomized, placebo-controlled trial in the EU indicated population (INNOVATE study) omalizumab significantly reduced oral corticosteroid use, exacerbation and total emergency visit rates, and significantly improved lung function, asthma symptoms and quality of life (11).

A comprehensive analysis of INNOVATE data found that it was difficult to predict which patients would gain greatest benefit from omalizumab based on pretreatment baseline characteristics; however, response to treatment could be reliably evaluated by a physician's overall assessment following an initial course of omalizumab (13). Of the 29 baseline variables assessed by the physician, only pretreatment total IgE was found to be broadly predictive of response in univariate and multivariate analyses. Lower total IgE was generally predictive of a lower response to omalizumab although

this was neither consistent across all eight response variables examined nor linearly related to increasing total IgE levels (13). A pooled analysis of data by IgE quartile (IU/ml: 0–75, 76–147, 148–273, ≥ 274) from seven clinical trials showed that omalizumab appeared to provide less benefit in patients with total IgE within the lowest quartile compared with patients with higher baseline total IgE levels (13). However, there were again inconsistencies across the clinical outcomes assessed.

If circulating allergen-specific IgE, rather than total IgE, is a key mediator in the pathogenic process for asthma, then allergen-specific IgE levels may explain why patients with low total IgE benefit less from treatment. An investigation into whether pretreatment total specific IgE in patients with low total IgE (a group in which omalizumab treatment has been shown to be less efficacious) is predictive of response to omalizumab, is therefore warranted. We assessed whether pretreatment specific IgE and related variables could be identified that were predictive of a response to omalizumab patients enrolled in the INNOVATE study. In addition we analysed data for patients with low total IgE (0–100 IU/ml) to assess whether pretreatment specific IgE load affected the reduction in free IgE following omalizumab treatment or was predictive of omalizumab response in these patients.

Methods

Patients and study design

Data from a randomized, placebo-controlled, double-blind clinical trial [INNOVATE study (11)] were analysed. All patients were skin-prick-test positive to at least one perennial aeroallergen and had pretreatment total IgE 30–700 IU/ml. All patients enrolled had inadequately controlled severe persistent allergic asthma despite high-dose ICS plus a LABA and additional controller medication if required. Patients were also required to demonstrate a forced expiratory volume in 1 second (FEV_1) ≥ 40 – $< 80\%$ of predicted normal value; overall mean FEV_1 was 61.0% of predicted normal value. Approximately 60% of patients were receiving additional controller medication (including maintenance oral corticosteroids [(22%), leukotrienes modifiers (35%) and theophyllines (27%)]), which was optimized prior to the 28 week treatment phase. Following an 8 week run-in period, patients were randomized to receive omalizumab or matching placebo for 28 weeks. Omalizumab was given as add-on therapy to concomitant asthma treatment and administered subcutaneously every 2 or 4 weeks according to patients' pretreatment bodyweight and baseline IgE levels using a dosing table (14).

Specific IgE

Levels of eight specific IgEs [six common perennial allergens (*Dermatophagoides pteronyssinus*; *Dermatophagoides farinae*; cat dander (E1); dog dander (E5); *Blatella germanica*; *Blatella orientalis*) and two mould allergens (*Aspergillus fumigatus*; *Alternaria alternata*)] and derived variables were determined (Table 1). The relationship between total IgE and total specific IgE load was also examined.

The relationship between total IgE according to omalizumab dosing table (14) [0–100 IU/ml (30–100 IU/ml in the dosing table); 100–200 IU/ml; 200–300 IU/ml; 300–500 IU/ml and > 500 IU/ml] and total specific IgE load was also analysed.

Baseline levels of specific IgE were determined using the commercially available Phadia fluoroimmunoassay ImmunoCAP (Phadia AB, Uppsala, Sweden). Values of specific IgE recorded as < 0.1 kU_A/l were treated as 0, and those > 100 kU_A/l were treated as 101 (for the assay used, the highest value validated by the manufacturer is 100). A commercially available microparticle enzyme immunoassay test kit (Abbot Inc., Abbott Park, IL, USA) was used to measure pretreatment total serum IgE.

Ability to predict response to omalizumab: univariate analysis

Univariate analyses were performed to assess the ability of the 20 specific IgE or derived variables to predict response to omalizumab. In the univariate analysis, 160 regression analyses were performed using the 20 specific IgE or derived variables as predictors for each of the eight response variables. The eight response variables included: number of exacerbations (asthma worsening requiring treatment with systemic corticosteroids); number of severe exacerbations (FEV_1 or peak expiratory flow $< 60\%$ of personal best and requiring systemic corticosteroids); exacerbation responder (no exacerbations); reduction in exacerbation rate from baseline (previous year) responder; severe exacerbation responder (no severe exacerbations); quality of life responder (≥ 0.5 improvement in overall Asthma Quality of Life Questionnaire overall score); physician's overall assessment responder (complete asthma control or a marked improvement) and FEV_1 responder (≥ 200 ml improvement in FEV_1). Poisson or logistic regression models were used for each response measure, as appropriate, and the interaction with specific IgE and derived variables determined.

Total specific IgE load in patients with total IgE 0–100 IU/ml

The relationship between baseline total specific IgE load and free IgE following omalizumab treatment was evaluated in those patients with total IgE 0–100 IU/ml, which corresponds to patients who fall into the first row of the omalizumab dosing table. Patients were subdivided into four quartiles of total specific IgE (upper, upper middle, lower middle and lower). Mean (95% CI) total free IgE after 12 weeks of treatment was calculated for each of the four quartiles. Mean (95% CI) total free IgE after 12 weeks of treatment was also calculated for patients classified into four quartiles according to total *Dermatophagoides*-specific IgE at baseline.

The ability of baseline total specific IgE load to predict response to omalizumab was assessed for each of the four total specific IgE quartiles. Response measures assessed were those used in the univariate analysis. For the two quantitative measures of response (exacerbation rate and severe exacerbation rate) data are provided as rate ratios versus placebo derived from Poisson regression. For the remaining six responder-type variables the number and percentage of patients responding according to each response criterion are presented.

Results

Specific IgE

Data were available for 337 patients; seven patients had a value for D1 and/or D2 above the assay limit and were

Table 1. Levels of specific IgE types and derived variables

Variable	n	Specific IgE kU _A /l					
		Mean	SD	Q25	Median	Q75	Range
D1	311	8.35	19.64	0	0.30	6.22	0–101§
D2	309	6.76	16.89	0	0.21	3.54	0–101§
E1	314	4.00	10.60	0	0.15	1.27	0–94.90
E5	315	2.91	7.34	0	0.24	2.02	0–73.00
I6	316	0.78	3.88	0	0	0.14	0–49.10
RI207	315	0.17	0.80	0	0	0	0–8.91
M3	316	0.65	2.46	0	0	0.20	0–29.40
M6	316	0.46	2.17	0	0	0.13	0–29.00
Total specific IgE*	318	23.60	39.56	0.63	6.00	27.96	0–206.03
D1:total IgE†	299	0.034	0.062	0	0.002	0.037	0–0.289
D2: total IgE†	297	0.027	0.053	0	0.001	0.023	0–0.264
E1 :total IgE†	302	0.018	0.042	0	0.001	0.012	0–0.288
E5:total IgE†	303	0.014	0.029	0	0.002	0.014	0–0.214
I6:total IgE†	304	0.004	0.021	0	0	0.001	0–0.226
RI207:total IgE†	303	0.001	0.004	0	0	0	0–0.052
M3:total IgE†	304	0.003	0.011	0	0	0.001	0–0.106
M6:total IgE†	304	0.003	0.012	0	0	0.001	0–0.110
Total IgE‡	337	202.5	152.7	74.0	151.0	307.0	21.0–632.0
Total IgE†	324	202.7	182.8	58.9	147.4	284.3	8.6–1291.4
Total specific IgE:total IgE†	306	0.102	0.126	0.006	0.050	0.151	0–0.738

D1: *Dermatophagoides pteronyssinus*; D2: *Dermatophagoides farinae*; E1: cat dander; E5: dog dander; I6: *Blatella germanica*; RI207: *Blatella orientalis*; M3: *Aspergillus fumigatus*; M6: *Alternaria alternata*.

*Total of the eight specific IgEs (total specific load).

†Measured at baseline (specific IgE values were measured only at baseline; however, mean total IgE levels were similar at screening and baseline).

‡Measured at screening.

§Seven patients had a value for D1 and/or D2 above the assay limit and were accounted for as 101 kU_A/l.

accounted for as 101 kU_A/l. Descriptive statistics for the 20 specific IgE and derived variables are shown in Table 1. All but three variables (total IgE at screening; total IgE at baseline; and ratio of total specific IgE to total IgE at baseline) are extremely skewed, with the mean exceeding the upper quartile while at least one quarter of the values are recorded as zero. This skewness does not invalidate the regression analyses that follow, but needs to be considered when interpreting the results. The two anti-*Dermatophagoides* IgEs (D1 and D2) made the major contribution to total specific IgE (means of 8.35 and 6.76 kU_A/l, respectively, out of the mean total of 23.60 kU_A/l), followed by IgEs specific to cat and dog danders (means of 4.00 and 2.91 kU_A/l, respectively, out of the mean total of 23.60 kU_A/l).

The two anti-*Dermatophagoides* IgEs (D1 and D2) were strongly related ($r = 0.83$) and had the strongest association with total specific IgE (Table 2). Levels of the two *Blatella*-specific IgEs (I6 and RI297; $r = 0.62$), and cat and dog dander-specific IgEs ($r = 0.63$) were also strongly related (Table 2). Each of the eight specific values correlated with its corresponding ratio to total specific IgE (0.83–0.96; data not shown).

Patients were tested for their response to each allergen and pair of allergens (Table 3). The majority of patients were positive to D1 *Dermatophagoides pteronyssinus* and D2 *Dermatophagoides farinae*. Patients positive to D1

were also highly likely to be positive to D2 and vice versa. For example, out of 171 patients positive to D1, 154 also tested positive to D2 (90%). Most patients had multiple sensitivities to several allergens tested. Relatively few patients were positive for either *Blatella* or moulds. Overall, 305 patients (90.5%) were sensitive to more than one allergen with 32 (9.5%) sensitive to only one [*Dermatophagoides* ($n = 20$); cat dander ($n = 8$), dog dander ($n = 2$), *Blatella* ($n = 2$)].

There was a strong correlation between total IgE and total specific IgE load (Fig. 1A). When assessed according to the levels of total IgE set out in the dosing table, the overall correlation between total IgE and total specific IgE load was seen in each of the five categories, and this was greatest in patients with total IgE 0–100 IU/ml. The ratio of total specific IgE load to total IgE was also positively correlated with total specific IgE load (Fig. 1B) and there was a negative relationship between this ratio and total IgE (data not shown).

Ability to predict response to omalizumab: univariate analysis

Table 4 summarizes all regressions that had a P -value ≤ 0.20 for the treatment-by-predictor interaction together with the direction of the variable (high or low) that apparently predicts most benefit from omalizumab. No interaction terms that had a $P \leq 0.20$ were obtained for

Table 2. Inter-relationship between specific allergens and total specific IgE load (Kendall rank correlation coefficient)*

	D1	D2	E1	E5	I6	RI207	M3	M6	Total specific IgE load
D1		0.83	0.20	0.30	0.30	0.31			0.64
D2			0.17	0.29	0.32	0.31			0.62
E1				0.63			0.17	0.16	0.47
E5							0.18	0.21	0.55
I6						0.62			0.28
RI207									0.24
M3								0.45	0.20
M6									0.21
Total specific IgE†									

D1: *Dermatophagoides pteronyssinus*; D2: *Dermatophagoides farinae*; E1: cat dander; E5: dog dander; I6: *Blattella germanica*; RI207: *Blattella orientalis*; M3: *Aspergillus fumigatus*; M6: *Alternaria alternata*.

*Only correlations that were significantly different from 0 at the $P < 0.001$ level are shown. Correlations > 0.60 are in bold.

†Total of the eight specific IgEs (total specific load).

Table 3. Percentage of patients positive to each allergen (0.35 kU_A/l) for which specific IgE was tested

Specific IgE variable	<i>n</i>	D1 <i>n</i> (%)	D2 <i>n</i> (%)	E1 <i>n</i> (%)	E5 <i>n</i> (%)	I6 <i>n</i> (%)	RI207 <i>n</i> (%)	M3 <i>n</i> (%)	M6 <i>n</i> (%)
D1	171		154 (90)	102 (60)	109 (64)	56 (33)	45 (26)	51 (30)	43 (25)
D2	165	154 (93)		97 (59)	109 (66)	56 (34)	44 (27)	50 (30)	41 (25)
E1	150	102 (68)	97 (65)		128 (85)	38 (25)	32 (21)	52 (35)	50 (33)
E5	161	109 (68)	109 (68)	128 (80)		44 (27)	37 (23)	54 (34)	53 (33)
I6	69	56 (81)	56 (81)	38 (55)	44 (64)		46 (67)	32 (46)	28 (41)
RI207	50	45 (90)	44 (88)	32 (64)	37 (74)	46 (92)		25 (50)	25 (50)
M3	82	51 (62)	50 (61)	52 (63)	54 (66)	32 (39)	25 (30)		47 (57)
M6	62	43 (69)	41 (66)	50 (81)	53 (85)	28 (45)	25 (40)	47 (76)	

D1: *Dermatophagoides pteronyssinus*; D2: *Dermatophagoides farinae*; E1: cat dander; E5: dog dander; I6: *Blattella germanica*; RI207: *Blattella orientalis*; M3: *Aspergillus fumigatus*; M6: *Alternaria alternata*.

cat dander (E1), *Blattella orientalis* (RI207) and the ratio of *Blattella germanica* (I6) to total IgE. Total IgE at screening was the variable with greatest predictive power followed by total IgE at baseline. Total specific load was not strongly predictive. Patients with relatively high values of D1 or D2, but with these making a relatively low contribution to total specific IgE load, appeared to attain most benefit from omalizumab.

Given that high levels of both *Dermatophagoides*-specific IgEs appear to be possible predictors of response, additional analyses were performed to investigate the predictive power of the sum of D1 and D2, as well as other combinations of these two values. These analyses improved predictive power and appeared to confirm that patients with high levels of D1- or D2-specific IgE but a low ratio to total IgE benefit most (data not shown); however, a robust predictor across multiple response variables could not be identified.

The two mould-specific IgEs (M3 and M6) made only small contributions to total specific load (Table 1), but it was patients with both relatively high values and relatively large contributions that gained most benefit. This is in contrast to the situation with the *Dermatophagoides*-specific IgEs. The cat and dog dander (E1 and E5) and *Blattella* variables (I6 and RI207) showed very

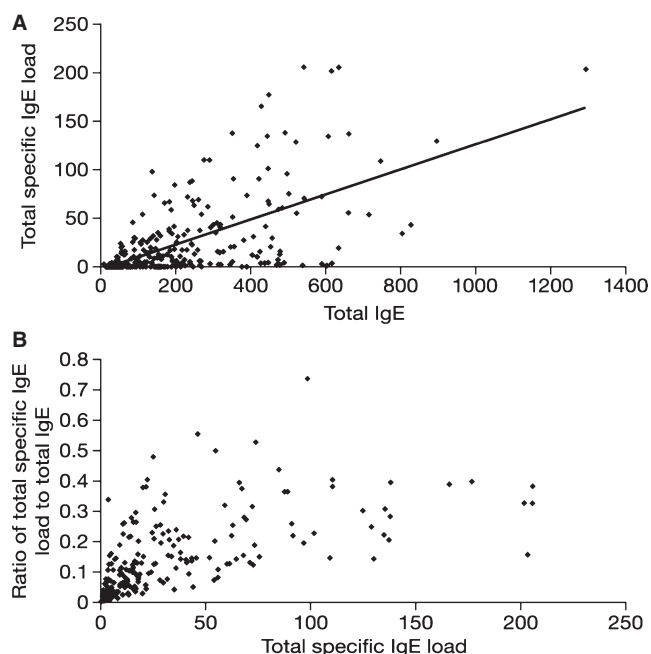


Figure 1. Relationship between total IgE and total specific IgE load (A) and between the ratio of total specific IgE load to total IgE and total specific IgE load (B).

Table 4. Interaction terms with $P \leq 0.20$ in univariate analyses

Specific IgE variable	P-value	Direction of most benefit from omalizumab
<i>D1</i>		
Exacerbation responder	0.103	High
<i>D2</i>		
Exacerbation responder	0.185	High
FEV ₁ responder	0.100	High
<i>E1</i>		
Physician's overall assessment responder	0.156	High
<i>I6</i>		
FEV ₁ responder	0.190	High
<i>M3</i>		
Number of exacerbations	0.196	High
Exacerbation responder	0.186	High
Quality of life responder	0.194	High
FEV ₁ responder	0.151	High
<i>M6</i>		
Number of exacerbations	0.099	High
Total specific IgE load*		
Exacerbation responder	0.116	High
<i>D1:total IgE†</i>		
Number of exacerbations	0.168	Low
Number of severe exacerbations	0.097	Low
Reduction in exacerbation rate responder	0.143	Low
Physician's overall assessment responder	0.162	Low
<i>D2:total IgE†</i>		
Number of exacerbations	0.107	Low
Reduction in exacerbation rate responder	0.196	Low
Physician's overall assessment responder	0.114	Low
FEV ₁ responder	0.126	High
<i>E1:total IgE†</i>		
Number of exacerbations	0.062	Low
Exacerbation responder	0.066	Low
Physician's overall assessment responder	0.016	High
<i>E5:total IgE†</i>		
Physician's overall assessment responder	0.199	High
<i>RI207:total IgE†</i>		
Exacerbation responder	0.198	Low
Quality of life responder	0.184	High
<i>M3:total IgE†</i>		
Number of exacerbations	0.079	High
Exacerbation responder	0.172	High
Reduction in exacerbation rate responder	0.137	High
<i>M6:total IgE†</i>		
Physician's overall assessment responder	0.101	High
Total IgE at screening		
Number of exacerbations	0.002	High
Exacerbation responder	0.075	High
Reduction in exacerbation rate responder	0.032	High
Quality of life responder	0.032	High
Physician's overall assessment responder	0.004	High
FEV ₁ responder	0.188	High
Total IgE at baseline		
Number of exacerbations	0.055	High
Exacerbation responder	0.118	High
Quality of life responder	0.094	High
Physician's overall assessment responder	0.084	High

Table 4. (Continued)

Specific IgE variable	P-value	Direction of most benefit from omalizumab
Total specific IgE load:total IgE		
Number of exacerbations	0.118	Low
Number of severe exacerbations	0.150	Low
Reduction in exacerbation rate responder	0.192	Low
FEV ₁ responder	0.148	High

D1: *Dermatophagoides pteronyssinus*; D2: *Dermatophagoides farinae*; E1: cat dander; E5: dog dander; I6: *Blatella germanica*; RI207: *Blatella orientalis*; M3: *Aspergillus fumigatus*; M6: *Alternaria alternate*.

*Total of the eight specific IgEs (total specific IgE load).

†Measured at baseline; $P < 0.05$ are in bold.

little predictive power and even the direction of most benefit is not consistent across the eight different methods of measuring benefit.

Total specific IgE load in patients with baseline total IgE 0–100 IU/ml

A total of 120 patients had baseline total IgE of 0–100 IU/ml and were included in these analyses. For total specific IgE load within this subgroup, the median value was 1.03, the lower quartile 0.11 and the upper quartile 4.55. These patients were subdivided into four equal subgroups ($n = 30$) by quartile of total specific IgE load (upper, upper middle, lower middle and lower quartile subgroups).

Relationship with free IgE following omalizumab treatment. There was little or no association between baseline total specific IgE load and mean total free IgE after 12 weeks of omalizumab. Mean (95% CI) free IgE was 8.82 (5.67, 11.97) for the lower quartile, 9.16 (6.24, 12.08) for the lower middle quartile, 7.80 (4.70, 10.90) for the upper middle quartile and 11.87 (8.49, 15.24) for the upper quartile. When baseline *Dermatophagoides*-specific IgE was similarly subdivided by quartile, similar data were obtained for the association with mean free IgE after 12 weeks of omalizumab. Mean (95% CI) free IgE was 7.16 (3.99, 10.33) for the lower quartile, 9.27 (6.37, 12.17) for the lower middle quartile, 8.53 (5.05, 12.01) for the upper middle quartile and 11.39 (8.31, 14.46) for the upper quartile. Omalizumab therapy suppressed total free IgE to the same degree irrespective of either total specific IgE or *Dermatophagoides*-specific IgE levels and well below the level associated with clinical efficacy (21 IU/ml).

Ability to predict response to omalizumab. The ability to predict response in terms of exacerbations and severe exacerbations varied according to total specific IgE quartiles. Rate ratio for exacerbation rates (omalizumab : placebo) were 2.345, 1.864, 0.367 and 1.740 for the upper, upper middle, lower middle and lower total specific IgE quartiles, respectively. Rate ratios for severe

exacerbations were 3.517, 0.497, 0.231 and 0.773, respectively. Although there was not a clear relationship, it appeared that patients with total specific IgE loads below the median gain the greatest response from omalizumab in terms of exacerbation rate, and patients with total specific IgE loads in the upper middle and lower middle quartiles gain most benefit in terms of severe exacerbation rate. However, it is important to note that there were only a small number of patients in each subgroup and exacerbation rate is an insensitive marker of response.

For the other six responder-type measures of response, the response rates within each quartile of total specific load showed inconsistencies of apparent effect between different response parameters (Table 5). For Exacerbation Responders and Reduction in Exacerbation Rate Responders, patients with total specific IgE load below the median appeared to gain most benefit from omalizumab, which was broadly consistent with the rate ratios for exacerbation rates. For Severe Exacerbation Responders, the responder rate defined on the basis of the severe exacerbation rate, patients in the middle two quartiles of total specific IgE load gained most benefit, which is consistent with the rate ratios for severe exacerbation rates.

For response defined in terms of quality of life, benefit was seen in all quartiles and was strongest in the two lower quartiles. In contrast, response according to the physician's overall assessment and FEV₁ showed most benefit in patients in the highest total specific IgE load quartile.

Discussion

This analysis found no consistent predictive effect for omalizumab response either for total specific IgE load or

for levels of individual allergen-specific IgE, either individually or in combination. Evaluation of IgE levels specific to individual allergens and their relationships to clinical benefit showed inconsistent effects between IgEs specific to different allergens, which would not be expected given the known mechanism of the disease process.

Although there were inconsistencies across response variables, pretreatment total IgE was found to be broadly predictive of response to omalizumab with least clinical benefit in patients with low pretreatment total IgE, which is consistent with an earlier analysis of INNOVATE data (13). Analyses focusing on the patients who appeared to show least clinical benefit (those with the lowest pretreatment total IgE; 0–100 IU/ml) found no consistent predictive effect of specific IgE level (either total specific IgE or total *Dermatophagoides*-specific IgE).

It was of interest that patients with high levels of *D. pteronyssinus*- or *D. farinae*-specific IgE but a low ratio to total IgE would appear to benefit most from omalizumab therapy; although this could not be statistically confirmed. Of note, it was not surprising that the majority of patients were positive to both *D. pteronyssinus* and *D. farinae* considering the high level of cross-reactivity observed between antigens extracted from *D. pteronyssinus* and *D. farinae* (15). It would be possible to analyse all patients ($n = 292$) who were allergic to *Dermatophagoides* in this study, regardless of their other allergies. However, this patient subpopulation is similar to the full patient population ($n = 337$) and the results would be predicted to be similar to the total specific IgE load analysis. Another interesting analysis would be to examine those patients who were only sensitive to *Dermatophagoides*; however, this subpopulation ($n = 20$) was too small to support a statistically valid assessment.

In addition, free IgE was reduced below target levels (21 IU/ml) irrespective of baseline total specific IgE in patients with low pretreatment total IgE (0–100 IU/ml) indicating target free IgE levels are attained in these patients irrespective of specific IgE load. It was not possible to examine the relationship between pretreatment total IgE and specific IgE following omalizumab treatment as there are no currently available assays. However, given that there is a strong positive correlation between pretreatment total IgE and pretreatment total specific IgE, particularly in patients with total IgE 0–100 IU/ml, and the fact that omalizumab binds all forms of circulating IgE, independent of its allergen specificity (16, 17), it could be expected that suppression of total IgE following omalizumab treatment would lead to a proportional reduction in total specific IgE.

These analyses demonstrate that whilst it cannot be excluded that specific IgE may play an important role, consistency across multiple response parameters could not be demonstrated to establish specific IgE as a robust predictor of response. When considering the results of this study, a few limitations should be noted. In line with

Table 5. Efficacy by total specific IgE quartile in patients with total IgE 0–100 IU/ml

Parameter	Quartile of total specific IgE load			
	Upper	Upper middle	Lower middle	Lower
Exacerbation responder				
Omalizumab	5/11 = 45%	6/13 = 46%	8/13 = 62%	8/13 = 62%
Placebo	15/18 = 83%	9/15 = 60%	7/15 = 47%	8/15 = 53%
Reduction in exacerbation rate responder				
Omalizumab	6/11 = 55%	7/13 = 54%	10/13 = 77%	8/13 = 62%
Placebo	16/18 = 89%	11/15 = 73%	8/15 = 53%	8/15 = 53%
Severe exacerbation responder				
Omalizumab	10/11 = 91%	12/13 = 92%	10/13 = 77%	11/13 = 85%
Placebo	17/18 = 94%	12/15 = 80%	9/15 = 60%	13/15 = 87%
Quality of life responder				
Omalizumab	6/11 = 55%	7/13 = 54%	9/13 = 69%	9/12 = 75%
Placebo	8/18 = 44%	7/15 = 47%	8/15 = 53%	6/13 = 46%
Physician's overall assessment responder				
Omalizumab	6/10 = 60%	5/13 = 38%	6/13 = 46%	4/11 = 36%
Placebo	6/17 = 35%	5/15 = 33%	6/15 = 40%	7/13 = 54%
FEV ₁ responder				
Omalizumab	6/11 = 55%	3/13 = 23%	2/13 = 15%	4/12 = 33%
Placebo	4/18 = 22%	6/15 = 40%	4/15 = 27%	6/14 = 43%

the omalizumab EU label, the INNOVATE study inclusion criteria were designed to include patients with severe persistent allergic asthma with impaired lung function, and establishing a predictor of response to omalizumab in this population is clearly valuable in clinical practice. However, the INNOVATE population was not selected on the basis of sensitivity to a particular allergen, and therefore the heterogeneous nature of patients' allergic sensitivities may give pause in drawing stronger conclusions. For example, a study in which patients were included on the basis of a single high specific-IgE level (e.g. house dust mites) across a broad range of asthma severity, and excluding those with lung function impairment due to nonallergic triggers, may reveal some pattern of predictive properties of specific IgE in relation to asthma response to omalizumab. Considering the demonstrated efficacy of omalizumab in combination with specific immunotherapy to treat grass pollen-allergic children (18), it might be expected that specific IgE would be a predictive marker of effectiveness. Other factors to bear in mind when interpreting results of this study are: several patients ($n = 7$) had a value above the specific IgE assay limit; specific IgE levels recorded in this study are skewed; specific IgEs against seasonal allergens were not analysed due to inadequate demographic and allergen season information. Additionally, results based on exacerbations need to be interpreted with caution and seen in the context of other endpoints, as exacerbations are infrequent events and the sample size available for analysis by quartiles was relatively small.

In conclusion, this analysis suggests that pretreatment total IgE was broadly predictive of response to omalizumab. In this analysis, allergen-specific IgE levels would appear not to provide a better prediction of response to treatment, do not allow better definition of the target population, and do not provide a way to refine dosing, as compared with total IgE levels. The current dosing table for omalizumab for patients with total IgE 30–700 IU/ml therefore appears to be the most suitable method to determine the correct prescribed dose. Taking into account that sensitivities and exposure to different allergens vary between patients and no strong and consistent signal was observed in the analyses presented here, we conclude that a physician's assessment following an initial course of omalizumab treatment is the most reliable method of identifying patients who respond to omalizumab. Further work is required to determine the utility of allergen-specific IgE levels in clinical practice.

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