

Total IgE and atopic status in patients with severe chronic spontaneous urticaria unresponsive to omalizumab treatment

To the Editor,

The humanized monoclonal anti-IgE antibody, omalizumab, has become a mainstay of the treatment of severe chronic spontaneous urticaria (CSU) based on the results of case series and phase III studies carried out during the last decade.^{1,2} However, although most patients respond to the drug, a proportion ranging between 7% and 48% CSU patients seem omalizumab-resistant.³ The reasons for this are still unclear, but the differences in clinical response to the treatment suggest that distinct pathways, all eventually leading to histamine release from mast cells and basophils, might play a pathogenic role in the disease. In view of the well-known mechanism of action of omalizumab, several recent studies have looked at the potential relevance of IgE in the pathogenesis of CSU. In effect, IgE autoantibodies specific for several autoantigens have been detected in CSU patients.⁴⁻⁶ Further, it has become increasingly clear that CSU patients responding to omalizumab show higher total IgE levels than nonresponders.⁷⁻¹⁰ However, considering that several CSU patients with high total IgE levels are nonresponders to omalizumab, it has not been possible to adopt this clinical laboratory parameter as a predictive factor of response so far. Since the atopic status is often associated with elevated levels of total IgE, in the present exploratory study we evaluated the role of atopic status in modifying the predictive value of total IgE levels for response to omalizumab in CSU naïve consecutive patients seen in 2 allergy centers for 2 years.

Seventy-six adults with severe, antihistamine-resistant CSU (mean age 48.2 years [range 22-76 years]; M/F 21/55; mean disease duration 59.3 months [range 2-600 months]; baseline UAS-7 score >30) treated with omalizumab 300 mg/month for at least 3 months as per the Italian Ministry of Health guidelines were studied. Baseline total IgE was

measured and expressed as kU/L (values <100 kU/L were considered normal), and atopic status was ascertained by clinical history and skin prick tests (SPT) with commercial extracts of the most common airborne allergens including pollens (grass, mugwort, ragweed, pellitory, plantain, birch, olive, cypress), house dust mites, molds (*Alternaria* spp.), and animal dander (cat and dog) either associated or not with a clinical history of respiratory allergy. SPT with commercial extracts of foods were carried out only in the presence of a clear-cut history of food allergy. Non-response to omalizumab was defined as the absence of any change (ie, >20%) in UAS-7 values 3 months after the start of the treatment. A fast response to omalizumab was defined as the disappearance or a reduction >50% of the UAS-7 score within 4 weeks after the first administration. A response was defined as slow if it occurred within 1 and 3 months after the first administration of the drug.

Based on the treatment outcome, patients were divided into responders ($n = 62$, including both fast [$n = 59$] and slow [$n = 3$] responders) and nonresponders ($n = 14$). The main clinical data of the two populations are shown in Table 1. The two subsets did not differ in terms of gender (M/F 18/44 vs 3/11, respectively), mean age (48.1 vs 48.5 years), mean disease duration (56.5 vs 71.9 months), and disease severity. Further, similar proportions of patients were atopic in the two subgroups (21/62 [34%] vs 6/14 [43%]; $P = \text{NS}$). When total IgE was analyzed, omalizumab responders and nonresponders did not differ significantly in baseline levels, although the levels in the former were on average higher (median [IQR], 183.5 [87-372] vs 58.5 [8-452] kU/L, respectively; $P = 0.07$, two-tailed Mann-Whitney U test). However, if atopic subjects were excluded from the analysis, omalizumab responders showed much higher total IgE levels (154 [78-281] kU/L) than patients nonresponding to omalizumab (21 [7.5-49] kU/L) ($P < 0.01$). In

TABLE 1 Clinical data of CSU patients responding and not responding to omalizumab treatment

	Responders	Nonresponders	P
No.	62	14	
Age in years (mean)	48.1	48.5	NS
Gender (M/F)	18/44	3/11	NS
Disease duration (months)	56.5	71.9	NS
Thyroid autoimmunity (%)	14 (23%)	5 (36%)	NS
Atopy (%)	34%	43%	NS
Total IgE in kU/L [median (IQR)]	183.5 (87-372)	58.5 (8-452)	NS (0.07)
Total IgE in nonatopic subjects	154 (78-281) $n = 41$	21 (7.5-49) $n = 8$	<0.01
Total IgE in atopic subjects	251 (124-555) $n = 21$	458.5 (264-607) $n = 6$	NS

NS, not significant.

order to analyse our data, we used a logistic regression approach, considering response to the treatment as the dependent variable. The c-statistic was used to evaluate the predictive ability of the models. We first fitted a logistic regression model to assess the role of the log-transformed IgE in predicting response to the treatment. We found a statistically significant effect of IgE ($P = 0.0149$) with a poor predictive ability (c-statistic = 0.652). To assess the role, as an effect modifier, of the atopic status of the patients in the ability of IgE to predict the response to the treatment, we subsequently fitted a logistic regression model including log-transformed IgE, atopic status, and the interaction between IgE and atopic status. All the effects in the model, including the interaction term ($P = 0.0044$), resulted statistically significant suggesting a role as effect modifier. Following this result, we assessed the predictive ability of IgE considering only the 49 nonatopic patients. We still obtained a statistically significant result ($P = 0.0037$) with an increased c-statistic value ($c = 0.928$) suggesting an excellent accuracy of IgE in predicting treatment response in atopic patients.

Interestingly, within the responders group, fast responders showed much higher mean total IgE levels (404 kU/L) than slow responders (112 kU/L) but the very little number of the latter subgroup ($n = 3$, two of which were atopic) hampered every meaningful statistical comparison.

Very recent studies showed that autoreactive IgE might play a role in the pathogenesis of CSU^{4–6} and that omalizumab responders are characterized by higher total IgE levels than subjects insensitive to the drug.^{7–10} In this study, possibly due to a limited number of patients included we were not able to confirm this finding, although nonresponders showed a much lower (albeit not statistically significant) median level of IgE. Since autoreactive IgE appear functionally active,⁵ these findings might represent a first step toward the understanding of the mechanism of action of anti-IgE therapy in a large proportion of CSU patients. However, total IgE levels show a large range of values among CSU patients with much overlap between omalizumab responders and nonresponders. By analyzing the atopic status of our CSU patients, we found that it acts as a factor modifying the ability of total IgE levels in predicting the response to omalizumab. In fact, while most (45/62 [73%]) omalizumab responders showed elevated baseline total IgE levels irrespective of their atopic status (86% among atopic subjects vs 66% among nonatopic subjects), all nonresponders to omalizumab showing total IgE levels exceeding 100 kU/L were atopic, while all nonatopic nonresponders showed very low total IgE levels. These observations indirectly support the idea that in CSU omalizumab might work by binding an autoreactive, functionally active IgE. By contrast, in patients nonresponding to the drug other pathogenic mechanisms leading to histamine release might be viable.

In conclusion, our data suggest that total IgE levels can be used as predictors of response to omalizumab in nonatopic CSU patients.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose regarding the present manuscript.

AUTHOR CONTRIBUTIONS

RA conceived the study. RA, SC, AVM, and MC recruited the patients and wrote the manuscript. GC performed the statistical analysis.

Keywords

atopy, IgE, omalizumab, urticaria

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Bronchial hyperresponsiveness in children with allergic rhinitis and the associated risk factors

To the Editor

Allergic rhinitis (AR) is the most common chronic allergic respiratory disease that become symptomatic after allergen exposure and commonly associated with asthma and/or sometimes with bronchial hyperresponsiveness (BHR).^{1,2} Bronchial challenges with methacholine or histamine are the most commonly used and better-standardized tests for quantifying BHR.² Most of the studies on relation of AR and BHR were done in adults.^{3,4} However, there is a need of further studies in childhood to uncover the actual prevalence of BHR in children with both coseasonal AR and preseasonal AR and the risk factors underneath.

In clinical practice, it is neither necessary nor possible to evaluate AR patients for BHR. But a practical clinical parameter would be valuable that render physicians to refer AR patients for lower airway evaluation. We therefore sought to evaluate in children

(age 6-18 years) with AR (intermittent or persistent) without any symptoms and history of asthma for the prevalence and risk factors for BHR and to detect a reliable, easily applicable, and cost-effective marker for identifying BHR in children with AR.

One hundred and eighty-six children diagnosed as AR in our outpatient clinic throughout 1-year period were consecutively recruited to the study. A detailed clinical history was taken and physical examination, skin prick tests, spirometry, and methacholine bronchial challenge tests (MBCT) were performed in all patients. Further details are available in the Data S1.

The median age of the patients was 12.7 (10.8-15.1) years, and the median age at onset of AR symptoms was 7 (5.5-9.5) years. The duration of AR was 60 (36-84) months. The demographic and general characteristics of the patients are shown in Table 1.

TABLE 1 Demographic characteristics and clinical and laboratory outcome measures of study population

	Whole study population (n = 186)	IAR (n = 146)	PAR (n = 40)	P value (IAR vs PAR)
Age(year) ^a	12.7 (10.8-15.1)	13.1(11-15.3)	11 (8.9-13)	0.001
Gender, n, M/F(M %)	117/69 (62.9%)	90/56 (61.6%)	13/27 (67.5%)	Ns
Onset age of AR symptoms (year) ^a	7 (5.5-9.5)	7.2 (6-9.5)	5.9 (4.1-8.1)	0.009
Duration of symptoms (month) ^a	60 (36-84)	60 (36-86)	48 (39-84)	Ns
Atopy index, n, %				
1	81, 43.5%	72, 49.4%	9, 22.5%	
2	53, 28.5%	37, 25.3%	16, 40%	
>2	52, 28%	37, 25.3%	15, 37.5%	
FEV1% ^b		96.63 (± 12)	93.25 (±10.65)	0.088
FEF 25-75 ^b		102.44 (± 23.26)	97.33 (±22.63)	Ns
Positivity of methacholine test n, %		45, 30.8%	18, 45%	0.093
PC20 in methacholine positive patients ^a		2 (1-5)	2 (0.5- 4)	Ns
Total IgE, kU/L ^a	177 (75-422)			
Eosinophil % ^a	3,9 (2.2-6.6)			
Eosinophil number, mm ^{3a}	300 (200-500)			
Atopic dermatitis, %	13.4%			
Atopy in the family, %	44.1%			
Exposure to cigarette, %	26.9%			

Ns, nonsignificant.

^aMedian (interquartile range).

^bMean (±SD).