Omalizumab is ineffective in regulating proasthmatic serum cytokine and chemokine levels in nonresponders with high BMI

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Agnes Yang, BS,[a]* Chao Gu, PhD,[a]* Katherine Upchurch, PhD,[b]* Adrien Caffiers, MS,[a] Mark Millard, MD,[c] Laurie Baert, PhD,[a] HyeMee Joo, PhD,[a,b] and SangKon Oh, PhD[a,b] *Scottsdale, Ariz; and Waco and Dallas, Tex*

Background: Omalizumab provides clinical benefits to a fraction of patients with asthma. It remains unclear why some patients do not respond to omalizumab therapy.

Objective: We sought to investigate whether omalizumab could alter serum cytokine and chemokine levels that could be associated with asthma pathogenesis. We also investigated why omalizumab is ineffective in controlling proasthmatic serum cytokine and chemokine levels in nonresponders.

Methods: Serum cytokine and chemokine levels in patients with moderate to severe asthma (N = 45; 34 responders and 11 nonresponders) were assessed before and after 26 weeks of omalizumab therapy. Correlations between cytokine and chemokine levels and asthma symptoms as well as characteristics of responders and nonresponders were assessed. Nonasthmatic subjects (N = 22) served as controls for patients with asthma (N = 45).

Results: Omalizumab was more effective in patients with increased serum eotaxin-1 and IL-13 levels than in others at baseline. Omalizumab decreased eotaxin-1 and IL-13, along with levels of most of the cytokines and chemokines tested, including IL-7, CCL17, and CXCL10, in responders, except for CCL5 and CCL22, which can contribute to neutrophilic and type 2 airway inflammation, respectively. In contrast, omalizumab did not decrease such serum cytokine and chemokine levels in nonresponders. Of interest, serum CCL17, CCL22, CXCL10, and IL-7 levels in nonresponders were associated with their body mass index, which could explain why omalizumab was unable to reduce their concentrations in nonresponders.

Conclusions: Omalizumab can regulate most cytokine and chemokine levels in responders. However, in nonresponders, it is unable to modulate specific proasthmatic cytokines and chemokines due to their association with individual body mass index, which is not influenced by omalizumab. (J Allergy Clin Immunol Global 2025;4:100462.)

Key words: *Asthma, IgE, anti-IgE, omalizumab, serum, cytokine, chemokine, body mass index*

Asthma is a chronic lung disease characterized by bronchial hyperreactivity, inflammation, bronchoepithelial damages, and airway obstruction. Although the pathophysiology of asthma remains unclear, serum IgE binding to a high-affinity IgE receptor (FcεRI) is one of the major events leading to its pathogenesis.[1,2] Neutralizing serum IgE with anti-IgE mAb (omalizumab, Xolair) can thus provide clinical benefits to patients with moderate to severe asthma.[3-5] However, a significant fraction of patients with asthma, ranging from 10% to 50%,[5-7] do not respond to omalizumab therapy. Such nonresponsiveness to omalizumab could be explained in part by the heterogeneity of asthma phenotypes and pathogenesis.[8,9] Nonetheless, understanding the mechanisms of action of omalizumab will further aid in the rational design of new therapeutics that can benefit a wider spectrum of patients with asthma. It could also improve the clinical efficacy of omalizumab by preselecting patients who would respond to omalizumab therapy.

Omalizumab does not crosslink FcεRI-bound IgE, which could induce the activation of mast cells and basophils. Instead, it binds to the Cε3 domain of free IgE, resulting in the prevention of IgE binding to FcεRI,[10,11] without binding FcεRI- or CD23 (FcεRII)-bound IgE.[5] By neutralizing free IgE in patient sera, omalizumab downregulates the surface expression of FcεRI on mast cells, basophils, and antigen-presenting cells.[12-14] IgE-free FcεRI is unstable and quickly internalized for degradation[15,16]; as such, FcεRI expression levels correlate with serum IgE levels.[17] Therefore, omalizumab limits IgE-mediated activation of mast cells and basophils, leading to reduced degranulation and secretion of proinflammatory mediators.[18-22] Decreased expression of FcεRI on antigen-presenting cells[12,13] could also limit IgE-bound allergen uptake followed by a decrease in allergen-specific type 2 inflammation. In a longitudinal analysis of whole blood transcripts of patients with asthma treated with omalizumab,[23] we previously found that both responders and nonresponders exhibited increased expression of transcripts associated with T_H2 (eg, *CSF3*, *IL4*, and *IL5*) and T_H1 responses (eg, *IFNG*, *STAT4*, and *SMARCR4*) compared with nonasthmatic controls. However, genes related to neutrophil activation and cytotoxicity were also enriched in omalizumab nonresponders.[23] We also reported that nonresponders, compared with responders, exhibited greater body mass index (BMI).[14]

In this study, we investigated whether omalizumab could differentially affect serum concentrations of cytokines and

From [a]the Department of Immunology, Mayo Clinic, Scottsdale; [b]the Institute for Biomedical Studies, Baylor University, Waco; and [c]Martha Foster Lung Care Center, Baylor University Medical Center, Dallas.

*These authors contributed equally to this study.

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Corresponding author: SangKon Oh, PhD, Department of Immunology, Mayo Clinic, 13400 East Shea Blvd, Scottsdale, AZ 85259. E-mail: oh.sangkon@mayo.edu.

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Abbreviations used
ACT: Asthma Control Test
BMI: Body mass index
hEGF: Human epidermal growth factor
hFGF-2: Human fibroblast growth factor 2

chemokines that are associated with the pathogenesis of asthma in responders and nonresponders. We found that omalizumab can regulate most of the serum cytokine and chemokine levels in responders. However, omalizumab was not effective in controlling them in nonresponders. Of interest, CCL17, CCL22, CXCL10, and IL-7 levels in nonresponders were found to be significantly associated with the BMI of individual patients. Data from this study suggest that omalizumab is less effective for obese patients with asthma than for nonobese patients, which is in line with our previously published data.[14]

METHODS

Subjects

Under the protocol approved by the institutional review board, 45 adult patients with moderate to severe asthma under treatment of inhaled corticosteroids and/or long-acting β2-adrenoceptor agonists were recruited. Disease severity was defined by a combination of low Asthma Control Test (ACT) score (<19), low lung function (as defined by FEV_1, score of <80% of predicted), and the frequency of symptoms, including total number of days with symptoms per week and of nighttime sleep disruption of more than once per week. This study excluded patients who were pregnant, younger than 18 years, and/or recently on omalizumab. Age- and sex-matched 22 nonasthmatic control subjects who had no history of allergic diseases, including asthma, atopic dermatitis, or food allergies, were also enrolled under the same protocol. All experiments were performed in accordance with the World Medical Association International Code of Medical Ethics (Declaration of Helsinki).

Study design

This single-arm intervention open-trial design was previously described.[23] In brief, patients were prescribed omalizumab (Xolair, provided by Genentech) on the basis of their physician's recommendation, dosed as per the manufacturer's dosing table according to the patient's serum IgE and body weight. All patients (N = 45) had asthma that was uncontrolled despite treatment with inhaled corticosteroids and/or long-acting β-agonists. Blood was collected 1 week before the initiation of treatment and again on the first day of treatment, before receiving omalizumab, and averaged as baseline samples. Once beginning treatment, blood samples were collected in week 6, week 14, and week 26 after the initiation of treatment.

At each blood draw, patients filled out the ACT questionnaire and an evaluation form for the total frequency of symptoms, inhaled steroid/β-agonist usages, and nighttime awakenings per week. A lung spirometer test was also performed.

Response to omalizumab was defined on the basis of improvements in asthma control, with nonresponders still exhibiting uncontrolled asthma, as previously described.[4,6,7,24,25] Asthma was considered to be not controlled if patients exhibited an ACT score of less than 19 with asthma symptoms, inhaled steroid/β-agonist usage at least twice per week, nighttime awakenings at least once per week, lack of change in asthma control medication, and having other indications of lack of asthma improvement confirmed by physicians, similar to other studies conducted analyzing omalizumab response.[6,7,24,25] Because lung function has not been shown to be an indicator of response to omalizumab,[26] it was not included in our responder classification. Table E1 (in the Online Repository available at www.jaci-global.org) presents summaries of omalizumab responders (N = 34) and nonresponders (N = 11), in comparison with nonasthmatic control subjects (N = 22), before and after omalizumab treatment.

Sera

Plasma was isolated from fresh whole blood by centrifugation. Serum was prepared with 10% thrombin (King Pharmaceuticals, Bristol, Tenn) and serum aliquots were stored at −80°C.

Serum cytokine and chemokine analysis

In addition to human epidermal growth factor (hEGF), human fibroblast growth factor-2 (hFGF-2), and soluble CD40L, 18 cytokines and chemokines in the serum were quantified using a Millipore multiplex array (EMD Millipore, Burlington, Mass) according to the manufacturer's instructions. The quantified cytokines and chemokines included GM-CSF, IFN-α, IL-3, IL-5, IL-7, IL-13, IL-17A, CCL2 (monocyte chemotactic protein-1), CCL4 (macrophage inflammatory protein-1β), CCL5 (RANTES), CCL8 (monocyte chemotactic protein-2), CCL11 (eotaxin-1), CCL13, CCL17 (thymus and activation-regulated chemokine), CCL22 (macrophage-derived cytokine), CXCL1 (growth-regulated oncogene), CXCL5 (epithelial cell–derived neutrophil activating peptide-78), CXCL10 (IFN-γ–induced protein-10), and CXCL13 (B-cell–attracting chemokine-1).

Statistical analysis

Statistical analyses were performed in GraphPad Prism 10 (GraphPad Software, San Diego, Calif). Correlation was tested with a simple linear regression test. Comparisons between different groups were made using the Mann-Whitney test, whereas comparisons between same groups before and after omalizumab treatment were made using the Wilcoxon matched pairs test. Data were presented as mean ± SD. The statistical significance was set at P less than .05.

RESULTS

Assessment of clinical outcomes of omalizumab therapy

The major characteristics of patients and nonasthmatic control subjects recruited in this study are summarized in Table I. Additional detailed information of responders and nonresponders is presented in Table E1. This study recruited 45 adult patients with moderate to severe asthma and 22 nonasthmatic control subjects. Of the 45 patients, 34 (76%) and 11 (24%) patients were determined as responders and nonresponders to omalizumab therapy, respectively.[23] At baseline, there was no significant difference between responders and nonresponders for asthma

TABLE I. Information of patients with asthma and nonasthmatic control subjects recruited in this study

Characteristics	Patients with asthma	Nonasthmatic controls
Total population, n	45	22
Age (y)	53.6 ± 1.9	41.6 ± 2.7
Sex: male/female (%male)	15/30 (33)	8/14 (36)
BMI	29.6 ± 1.0	24.6 ± 0.8
Past smoker, n (%)	13 (29)	NA
Race, n (%)		
White	41 (91)	17 (77)
Black	3 (7)	4 (18)
Asian	1 (2)	1 (5)

Data are presented as mean ± SEM, where applicable.
NA, Not applicable/available.

symptoms, ACT score, and the frequency of oral corticosteroid, inhaled corticosteroid, leukotriene inhibitor, and β-agonist usages as well as lung functions tested by measuring FEV_1, forced vital capacity, and forced expiratory flow at 25% to 75% of forced vital capacity. By week 26 (≥6 months) of omalizumab therapy, responders had increased ACT scores, with reduced total numbers of symptoms and nighttime awakenings. Most (30 of 34) responders exhibited a reduction in clinical symptoms by week 14 of treatment. Characteristics of nonasthmatic control subjects (N = 22) are also presented in Table E1.

Patients with asthma have altered serum cytokine and chemokine levels

Before investigating the effects of omalizumab on serum cytokine and chemokine levels, we first compared the levels of hEGF, hFGF-2, and soluble CD40 ligand, along with 6 cytokines and 12 chemokines, in the sera of patients with asthma with those in nonasthmatic control subjects (Table II). Of these 21 analytes, 6 analytes were found to be significantly altered in the sera of patients with asthma. Patient sera had elevated levels of hFGF-2 and certain cytokines (GM-CSF and IL-7) and chemokines (CCL4 and CXCL13), whereas they had decreased levels of eotaxin-1. It was also of note that, except for CCL4, CCL11, and CXCL13, the differences between patients and control subjects were largely dependent on a few specific donors (Fig E1). There were no significant alterations in other analytes, including hEGF, soluble CD40 ligand, and some of the cytokines (IL-5, IL-13, IL-17A, and IFN-α) and chemokines (CCL2, CCL8, CXCL10, CCL17, CCL22, CXCL1, and CXCL5) tested. We were not able to detect significant amount of IL-4 in patient sera tested. Therefore, we concluded that patients with moderate to severe asthma had altered serum levels of hFGF-2 and some of the cytokines (GM-CSF and IL-7) and chemokines (eotaxin-1, CCL4, and CXCL13) that could be associated with the pathogenesis of asthma.[27-34]

Omalizumab decreases serum cytokine and chemokine levels in responders

To examine the effect of omalizumab treatment on serum cytokine and chemokine levels, we first compared the baseline levels of serum cytokines and chemokines in omalizumab responders with those of nonresponders (Table III; see Fig E2 in this article's Online Repository at www.jaci-global.org). Of interest, responders had elevated serum eotaxin-1 and IL-13 levels, which are associated with type 2 inflammation.[35,36] In line with the increased serum eotaxin-1 and IL-13 levels, responders also had higher average eosinophil counts than nonresponders at baseline, but the difference was not significant (see Fig E3, *A*, in this article's Online Repository at www.jaci-global.org). A similar observation was made at week 26 as well (Fig E3, *B*). In addition, omalizumab did not significantly alter the frequency of eosinophils in the blood (Fig E3, *C*).

We next investigated whether omalizumab could affect serum cytokine and chemokine levels, including IL-7, GM-CSF, eotaxin-1, CCL4, CXCL13, and hEGF2, that were higher in patients with asthma than in control subjects. We found that not only the levels of these 6 proteins (IL-7, GM-CSF, eotaxin-1, CCL4, CXCL13, and hEGF2) were altered, but also serum levels of many others (hFGF-2, IL-5, IL-13, CCL2, CCL5, CCL11, CCL13, CCL17, CXCL1, CXCL5, and CXCL-10) were significantly decreased in responders at week 26 (Table IV; see Fig E4 in this article's Online Repository at www.jaci-global.org). However, omalizumab was not capable of reducing serum CCL22 (macrophage-derived chemokine) and CCL5 (RANTES) levels in either responders (Table IV and Fig E4) or nonresponders (Table IV; see Fig E5 in this article's Online Repository at www.jaci-global.org), suggesting that clinical benefits provided by omalizumab might not be through the decrease in serum CCL22 and/or CCL5 levels. Nonetheless, omalizumab can still decrease serum eotaxin-1 and IL-13 as well as IL-5 and CCL17, which can promote type 2 lung inflammation. Such decreases were observed only in responders. In addition to CCL17, CCL22 is a proallergic T_H2-type chemokine.[31,37,38] CCL5 also promotes neutrophilic inflammation while paradoxically correlating with type 2 airway inflammation and sputum eosinophilia.[39]

In contrast to the effects of omalizumab treatment in responders, none of the serum cytokines or chemokine levels were significantly decreased in nonresponders (bottom, Table IV and Fig E5).

Taking these data together (Tables III and IV and Figs E4 and E5), we concluded that sera of responders contain elevated levels of type 2 inflammatory markers (eotaxin-1 and IL-13) at baseline. At week 26, however, we found that not only eotaxin-1 and IL-13 levels, but also serum levels of most cytokines tested were decreased in responders, but not in nonresponders. Despite this, omalizumab was not able to regulate serum CCL22, a T_H2 chemokine, and CCL5, which are capable of promoting type 2 and neutrophilic lung inflammation.

Omalizumab cannot control BMI-associated serum CCL17, CCL22, CXCL10, and IL-7 levels in nonresponders

Compared with responders, nonresponders relatively well maintained their serum cytokine and chemokine levels after omalizumab treatment. This suggested that nonresponders could possess characteristics that distinguish them from responders, which allow them to maintain serum levels of cytokines and chemokines.

Of interest, we found that serum CCL17 (Fig 1, *A*) and CXCL10 (Fig 1, *B*) levels correlated with the BMI of nonresponders at week 26. We also found that serum CCL22 (Fig 1, *C*) and IL-7 (Fig 1, *D*) levels in nonresponders correlated with

TABLE II. Comparison of the levels of cytokines and chemokines in the baseline sera of patients with asthma (N = 45) and nonasthmatic control subjects (N = 22)

Cytokines and chemokines	Nonasthmatic controls (pg/mL)	Patients with asthma (pg/mL)	Significance
hEGF	112 (0-212)	124 (26-781)	NS
hFGF-2	173 (23-1,671)	197 (17-2,196)	*
sCD40L	1,185 (142-4,689)	1,699 (0.41-5,652)	NS
GM-CSF	15 (0-73)	95 (0.85-2,278)	†
IFN-α	25 (0-274)	40 (0-476)	NS
IL-5	6 (0.5-60)	7 (0-92)	NS
IL-7	11 (0-48)	29 (0-335)	†
IL-13	58 (0-576)	78 (0-890)	NS
IL-17A	59 (0-384)	76 (0-1,011)	NS
CCL2 (MCP-1)	439 (57-632)	502 (166-1,002)	NS
CCL4 (MIP-1β)	68 (0-484)	102 (20-660)	‡
CCL5 (RANTES)	68,886 (29,655-1,71,347)	78,033 (0-2,26,121)	NS
CCL8 (MCP-2)	21.78 (8-44)	26 (7-55)	NS
CCL11 (Eotaxin-1)	168 (42-331)	117 (21-319)	*
CCL13	59 (5-148)	41 (5-125)	NS
CCL17 (TARC)	63 (5-112)	79 (8-274)	NS
CCL22 (MDC)	482 (224-1,181)	630 (118-4,457)	NS
CXCL1 (GRO)	3,266 (709-7,454)	9,693 (393-1,44,313)	NS
CXCL5 (ENA-78)	1,090 (256-2,631)	1293 (99-4,051)	NS
CXCL10 (IP-10)	239 (124-511)	252 (36-1,023)	NS
CXCL13 (BCA-1)	14 (2-94)	23 (6-119)	*

Data are expressed as mean (range). Mann-Whitney test was used to determine significant difference.
BCA-1, B-cell–attracting chemokine-1; *ENA-78*, epithelial cell–derived neutrophil activating peptide-78; *GRO*, growth-regulated oncogene; *IP-10*, IFN-γ–induced protein 10; *MCP-1*, monocyte chemoattractant protein 1; *MCP-2*, monocyte chemoattractant protein 2; *MDC*, macrophage-derived chemokine; *MIP-1β*, macrophage inflammatory protein-1β; *NS*, not significant; *sCD40L*, soluble CD40 ligand; *TARC*, thymus and activation-regulated chemokine.
*$P < .01$.
†$P < .05$.
‡$P < .001$.

BMI at baseline. Such correlations were not found in responders. These data (Fig 1) are in line with our previously published data,[14] showing that the outcomes of omalizumab treatment were significantly affected by the BMI of individual patients with asthma. It has been well known that serum concentrations of CCL17, CCL22, CXCL10, and IL-7 correlate with BMI.[40-43] None of the other patient characteristics, including age and serum IgE level, were associated with their serum concentrations.

To further test the biological relevance of our findings in Fig 1, we next tested whether any specific cytokines and/or chemokines in Fig 1 could also be directly associated with asthma symptoms by measuring correlations between the serum concentrations of these 4 analytes and ACT scores at week 26. As shown in Fig 2, *A*, serum IL-7 levels inversely correlated with ACT scores of nonresponders at week 26. Such correlation was not observed in responders. Serum CCL17 (Fig 2, *B*), CCL22 (Fig 2, *C*), and CXCL10 (Fig 2, *D*) also showed similar trends, but not statistically significant, which is warranted to be further studied in the future.

Taking these data together (Figs 1 and 2), we concluded that serum concentrations of IL-7, CCL17, CCL22, and CXCL10 in nonresponders are linked to the BMI of nonresponders. As a result, omalizumab cannot effectively regulate serum levels of these cytokines and chemokines in patients with high BMI, which can continue to exacerbate clinical symptoms of asthma.

DISCUSSION

Omalizumab is one of the mainstays of therapy for patients with moderate to severe asthma. Given the heterogeneity of asthma, it is unsurprising to observe that omalizumab provides only a fraction of patients with asthma with improved clinical benefits.[5-7] Finding key biological variables that can determine response to omalizumab either at baseline or after treatment will advance our understanding of its mechanisms of action. It will also provide us an opportunity to improve clinical benefits by identifying patients who are likely to respond to omalizumab therapy.

Elevated serum levels of hFGF-2, GM-CSF, IL-7, CCL4, and CXCL13 in patients are associated with the pathogenesis of asthma,[27-34] although hFGF-2 secreted by damaged airway epithelial cells promotes airway inflammation.[27] Both GM-CSF[28,30] and IL-7[31] contribute to allergic asthma through the enhancement of allergen-specific T_H2 response. GM-CSF not only accelerates the growth and maturation of eosinophils but also primes them for activation, and enhances their survival.[44,45] CCL4[33] and CXCL13[34] are also involved in eosinophilic asthma and allergic airway inflammatory process.[46] In contrast to the data in the previous study,[47] we found that patients with asthma had decreased serum levels of eotaxin-1 when compared with nonasthmatic controls. According to Tateno et al,[48] although serum eotaxin-1 levels can be affected by corticosteroid, plasma eotaxin-1 level was still correlated with the severity of asthma. Patients receiving both inhaled and oral corticosteroid had elevated serum eotaxin-1 levels compared with those receiving no corticosteroids or only inhaled corticosteroid treatment.[48] Nonetheless, such decreased serum eotaxin-1 levels in patients with asthma remain to be further investigated, as eotaxin-1 plays a pivotal role in the pathogenesis of asthma, including airway remodeling.[32]

TABLE III. Baseline serum cytokine and chemokine levels in omalizumab responders (N = 34) and nonresponders (N = 11)

Cytokines and chemokines	Responders (pg/mL)	Nonresponders (pg/mL)	Significance
hEGF	131 (26-781)	104 (26-187)	NS
hFGF-2	231 (17-2,196)	93 (36-200)	NS
sCD40L	1,782 (43-5,652)	1,451 (0.41-3,043)	NS
GM-CSF	121 (0.85-2,278)	15 (0.85-60)	NS
IFN-α	48 (0-476)	13 (0-42)	NS
IL-5	8 (0-92)	4 (0-19)	NS
IL-7	34 (0-335)	13 (5-29)	NS
IL-13	103 (0-890)	2 (0-10)	*
IL-17A	91 (0-1,011)	33 (3-85)	NS
CCL2 (MCP-1)	493 (166-1,002)	527 (254-848)	NS
CCL4 (MIP-1β)	115 (22-660)	61 (20-196)	NS
CCL5 (RANTES)	74,202 (0-2,26,121)	89527 (17,760-1,69,945)	NS
CCL8 (MCP-2)	27 (7-55)	23 (14-43)	NS
CCL11 (Eotaxin-1)	129 (21-319)	81 (30-138)	*
CCL13	45 (5-125)	29 (7-99)	NS
CCL17 (TARC)	86 (11-274)	56 (8-129)	NS
CCL22 (MDC)	685 (118-4,457)	467 (218-824)	NS
CXCL1 (GRO)	9935 (944-1,44,313)	8896 (393-54,127)	NS
CXCL5 (ENA-78)	1,171 (99-4,051)	1658 (410-2,674)	NS
CXCL10 (IP-10)	248 (36-1,023)	264 (107-408)	NS
CXCL13 (BCA-1)	27 (6-119)	13 (6-26)	NS

Data are expressed as mean (range). Mann-Whitney test was used to determine significant difference.
BCA-1, B-cell–attracting chemokine-1; *ENA-78*, epithelial cell–derived neutrophil activating peptide-78; *GRO*, growth-regulated oncogene; *IP-10*, IFN-γ–induced protein 10; *MCP-1*, monocyte chemoattractant protein 1; *MCP-2*, monocyte chemoattractant protein 2; *MDC*, macrophage-derived chemokine; *MIP-1β*, macrophage inflammatory protein-1β; *NS*, not significant; *sCD40L*, soluble CD40 ligand; *TARC*, thymus and activation-regulated chemokine.
*$P < .05$.

In a direct comparison between omalizumab responders and nonresponders, we found that responders had elevated serum eotaxin-1 and IL-13 levels at baseline, suggesting heightened type 2 inflammation[49,50] in responders. IL-13 and other T_H2 cytokines can induce eotaxin-1 expression by various cell types, including eosinophils, B cells, fibroblasts, endothelial cells, macrophages, and airway smooth muscle cells.[36,51] Elevated serum IL-13 levels also support the clinical feature of severe asthma.[52]

In addition to CXCL1 and CXCL5, omalizumab therapy decreased the levels of serum hEGF, hFGF-2, cytokines (GM-CSF, IL-5, IL-7, and IL-13), and chemokines (eotaxin-1, CCL2, macrophage inflammatory protein-1β, CCL5, CCL8, CCL13, CCL17, and CXCL10) in responders. Both CCL17 and CCL22 are proallergic chemokines,[31,37,38] but omalizumab decreased serum CCL17 levels only in responders. In contrast to the previously published data,[53] we found that omalizumab did not significantly alter serum CCL5 levels in either responders or nonresponders. CCL5 (RANTES) contributes to a neutrophilic inflammation while also being correlated with type 2 inflammation[39] by modulating cytokine production. CCL5 can induce a switch from T_H2-type to T_H1-type cytokines,[54] as well as the up-regulation of T_H1 cytokines (IL-2 and IFN-γ) and T_H2 cytokines (IL-5).[55] Although Maggi et al[50] reported that omalizumab decreased CD154 (CD40L) expression on $CD4^+$ T cells, there were no significant alterations in soluble CD40L in the sera of responders or nonresponders in our study.

Compared with control subjects, patients with asthma exhibited altered serum cytokine and chemokine levels. Nonetheless, such alterations could also be caused, at least in part, by medications including corticosteroid and β-agonists. When comparing responders and nonresponders, there was no significant difference in the usage of medications by the 2 groups of patients with asthma at baseline. However, during and after treatment with omalizumab, some of the patients, particularly responders, took fewer medications than nonresponders, which might also affect the serum cytokine and chemokine levels at week 26. Regardless of the potential effects of medications, serum CCL5 and CCL22 levels were well maintained throughout omalizumab treatment without any significant alteration in both responders and nonresponders. This suggests that clinical benefits provided by omalizumab are not attributable to reductions in levels of serum CCL22 and/or CCL5, which are known to promote type 2 airway inflammation.[31,37-39]

Currently, there are limited explanations for the variable response to omalizumab treatment observed across patients. Some predictors of response to omalizumab suggested by previous studies include blood eosinophil count and serum IgE level,[56,57] smoking status and ages,[58] chronic urticaria symptoms,[59] and BMI[58,60] of patients.[61,62] Of these, our results corroborate with BMI being a potential predictor of treatment response. Our findings on the potential roles of serum CCL17, CCL22, CXCL10, and IL-7 in the pathogenesis of asthma, especially in nonresponders, are important because their serum levels are not affected by omalizumab therapy, but more so by the BMI of individual nonresponders. This suggests that any therapeutic strategy targeting these 4 factors might not be effective in obese patients with asthma. Indeed, we previously reported that BMI was higher in nonresponders than in responders.[14] In support of our observation in this study, it is also well known that serum IL-7, CCL17, CCL22, and CXCL10 levels correlate with BMI.[40-43] A recent study[63] reported that omalizumab responders showed increased plasma CXCL10 levels with CXCL10/CCL17 ratio. In our study, however, CXCL10 levels were similar in both responders and nonresponders (Table III

TABLE IV. Omalizumab treatment alters serum cytokine and chemokine levels in responders (N = 34), but not in nonresponders (N = 11)

Cytokines and chemokines	Responders baseline (pg/mL)	Responders week 26 (pg/mL)	Significance
hEGF	131 (26-781)	128 (25-666)	*
hFGF-2	231 (17-2,196)	202 (10-2,168)	†
sCD40L	1,782 (43-5,652)	1,441 (59-3,925)	NS
GM-CSF	121 (0.85-2,278)	100 (0-2,092)	†
IFN-α	48 (0-476)	46 (0-424)	NS
IL-5	8 (0-92)	4 (0-31)	*
IL-7	34 (0-335)	34 (0-454)	†
IL-13	103 (0-890)	95 (0-875)	*
IL-17A	91 (0-1,011)	91 (0-962)	NS
CCL2 (MCP-1)	493 (166-1,002)	441 (124-830)	†
CCL4 (MIP-1β)	115 (22-660)	243 (12-4,513)	†
CCL5 (RANTES)	78,684 (0-2,26,121)	80,218 (1,750-7,55,815)	NS
CCL8 (MCP-2)	27 (7-55)	21 (0-39)	‡
CCL11 (Eotaxin-1)	129 (21-319)	116 (12-278)	*
CCL13	45 (5-125)	38 (6-119)	§
CCL17 (TARC)	86 (11-274)	73 (7-348)	†
CCL22 (MDC)	685 (118-4,457)	659 (64-3,658)	NS
CXCL1 (GRO)	9,935 (944-1,44,313)	3,424 (634-1,14,60)	†
CXCL5 (ENA-78)	1171 (99-4,051)	916 (92-2,384)	†
CXCL10 (IP-10)	248 (36-1,023)	192 (20-477)	*
CXCL13 (BCA-1)	27 (6-119)	21 (0-125)	§

Cytokines and chemokines	Nonresponders baseline (pg/mL)	Nonresponders week 26 (pg/mL)	Significance
hEGF	103 (26-187)	90 (38-169)	NS
hFGF-2	93 (36-200)	111.81 (11-456)	NS
sCD40L	1,451 (0.41-3,043)	2,057 (0.41-5,766)	NS
GM-CSF	15 (0.85-60)	16 (0.54-60)	NS
IFN-α	13 (0-42)	17 (0-44)	NS
IL-5	4 (0-19)	3 (0-18)	NS
IL-7	13 (5-29)	9 (3-23)	NS
IL-13	2 (0-10)	1 (0-8)	NS
IL-17A	33 (3-85)	62 (3-437)	NS
CCL2 (MCP-1)	527 (254-848)	526 (216-1,070)	NS
CCL4 (MIP-1β)	61 (20-196)	53 (19-21,198)	NS
CCL5 (RANTES)	89,527 (17,760-1,69,945)	71,209 (3,167-2,21,516)	NS
CCL8 (MCP-2)	23 (14-43)	22 (11-53)	NS
CCL11 (Eotaxin-1)	81 (30-138)	70 (23-139)	NS
CCL13	29 (7-99)	28 (5-97)	NS
CCL17 (TARC)	57 (8-129)	49 (11-133)	NS
CCL22 (MDC)	467 (218-824)	485 (136-951)	NS
CXCL1 (GRO)	3,870 (393-54,127)	2,526 (465-6,742)	NS
CXCL5 (ENA-78)	1,658 (410-2,674)	1,431 (342-2,793)	NS
CXCL10 (IP-10)	264 (107-408)	310 (97-63)	NS
CXCL13 (BCA-1)	13 (6-26)	19 (5-117)	NS

Data are expressed as mean (range). Wilcoxon matched pairs test was used to determine significant difference.
BCA-1, B-cell–attracting chemokine-1; *ENA-78*, epithelial cell–derived neutrophil activating peptide-78; *GRO*, growth-regulated oncogene; *IP-10*, IFN-γ–induced protein 10; *MCP-1*, monocyte chemoattractant protein 1; *MCP-2*, monocyte chemoattractant protein 2; *MDC*, macrophage-derived chemokine; *MIP-1β*, macrophage inflammatory protein-1β; *NS*, not significant; *sCD40L*, soluble CD40 ligand; *TARC*, thymus and activation-regulated chemokine.
*$P < .05$.
†$P < .01$.
‡$P < .0001$.
§$P < .001$.

and Fig E2) while omalizumab treatment decreased both CXCL10 and CCL17 in responders. Because both serum CXCL10 and CCL17 levels are associated with BMI, these data might need to be further validated by performing experiments with increased numbers of obese and nonobese patients with asthma in future studies.

Although this study offers valuable insights for the mechanisms of action of omalizumab, several limitations must be considered. This exploratory study was not designed with a predefined sample size. Therefore, data from this study are not confirmatory. With a relatively small sample size (N = 45), it is possible that potential outliers could affect the

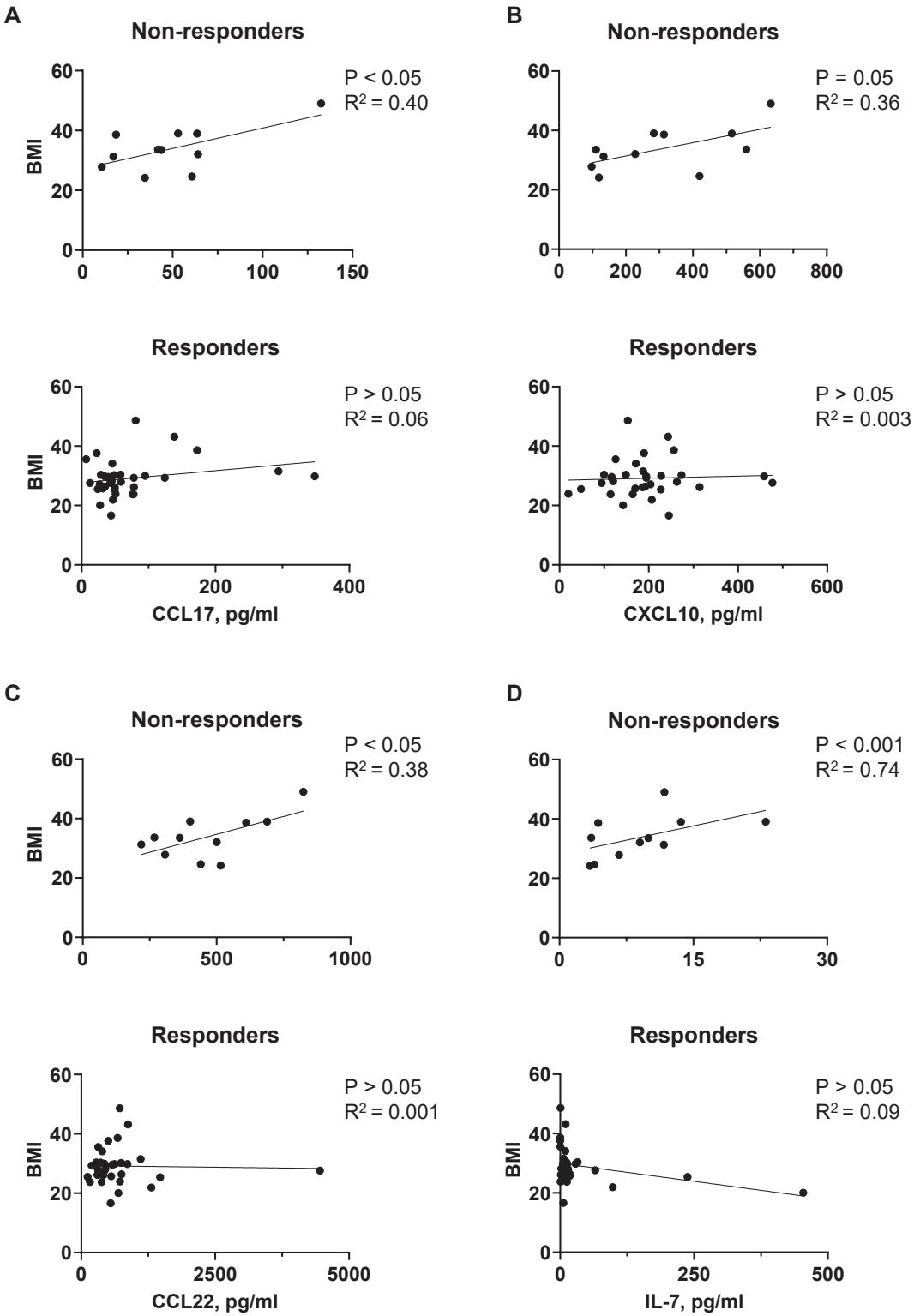

FIG 1. Serum levels of CCL17 (**A**) and CXCL10 (**B**) at baseline as well as CCL22 (**C**) and IL-7 (**D**) at week 26 correlate with the BMI of nonresponders (N = 11), but not responders (N = 34). Simple linear regression test was used to determine significance.

study conclusions. In addition, this study did not account for the potential effects of coexisting allergic diseases, highlighting the need for larger-scale studies with better defined patients. Type 2 inflammatory markers are also known to be elevated in other allergic conditions, such as atopic dermatitis.[64]

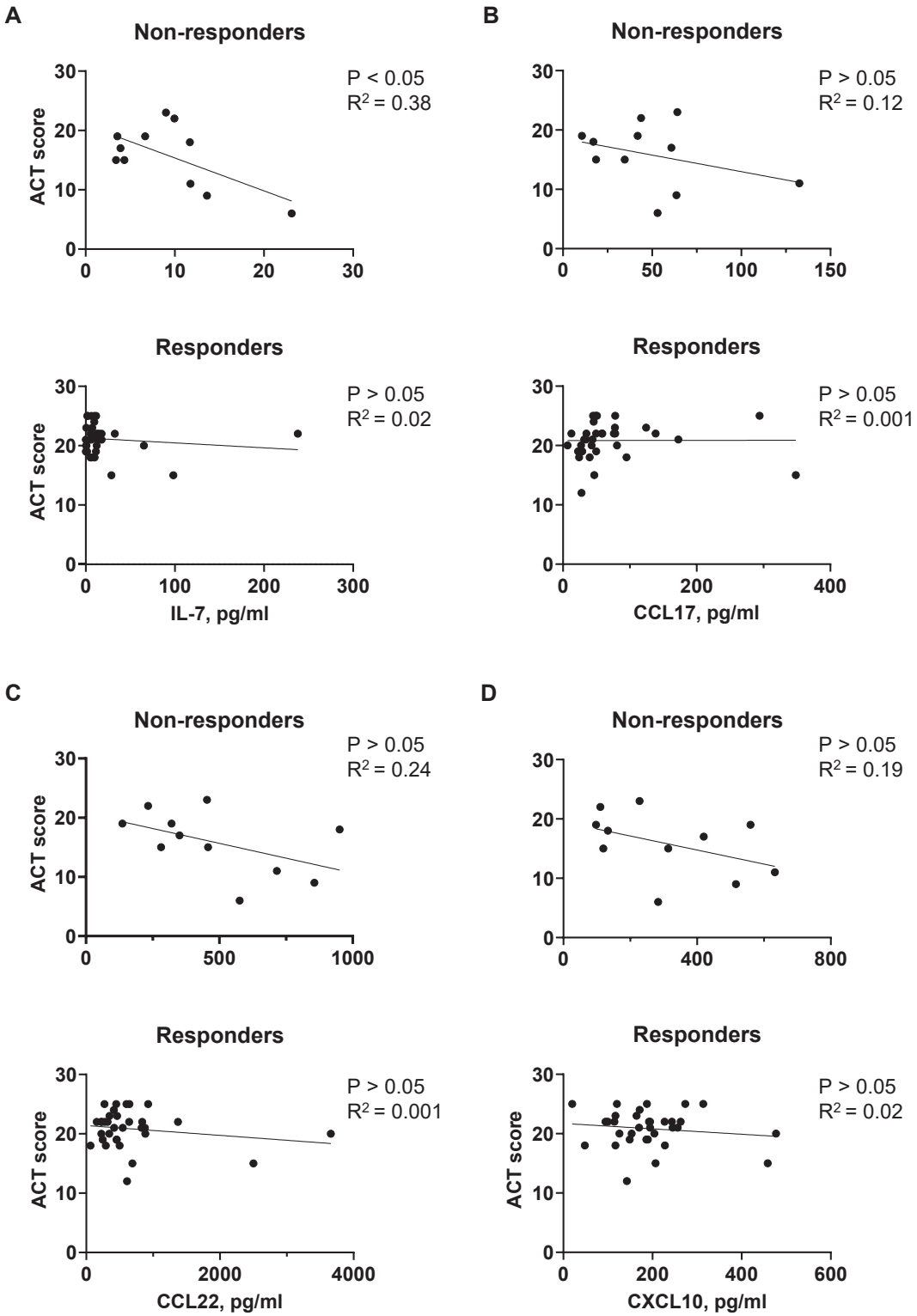

FIG 2. Serum IL-7 level (**A**) at week 26 inversely correlates with ACT scores of nonresponders (N = 11), but not responders (N = 34). Correlations between ACT scores and serum CCL17 (**B**), CCL22 (**C**), and CXCL10 (**D**) levels at week 26 are also presented. Simple linear regression test was used to determine significance.

In summary, omalizumab decreased not only serum eotaxin-1 and IL-13 levels, but also other proallergic and asthmatic cytokines and chemokines in responders, except for CCL22 and CCL5 (RANTES), which can contribute to type 2 and neutrophilic inflammation in the lung, respectively. However, omalizumab could not effectively control serum levels of these cytokines

and chemokines in nonresponders. In particular, serum levels of CCL17, CCL22, CXCL10, and IL-7 in nonresponders were associated with the BMI of individual patients, which could not be controlled by omalizumab. Therefore, this study enhances our understanding of the mechanisms of action of omalizumab and further aids in the ability of clinicians to identify patients who may benefit from omalizumab treatment.

DISCLOSURE STATEMENT

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Key messages

- **Omalizumab can control most proallergic and asthmatic serum cytokine and chemokine levels, except for CCL5 and CCL22, in responders.**
- **Omalizumab cannot control BMI-associated serum cytokine and chemokine levels in nonresponders.**
- **Omalizumab could thus be less effective for obese patients with asthma than for nonobese patients with asthma.**

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