

The effect of omalizumab treatment on the low affinity immunoglobulin E receptor (CD23/fc epsilon RII) in patients with severe allergic asthma

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ABSTRACT

Background: Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody used in the treatment of severe asthma. Its therapeutic efficacy is primarily attributed to reduction of serum-free IgE and in the expression of high-affinity IgE receptor, fc epsilon RI. However, its effect on the low-affinity IgE receptor fc epsilon RII/CD23 *in vivo* has not been evaluated.

Aim: To determine whether CD23 plays a role in the inflammatory process in severe uncontrolled asthma and whether anti-IgE therapy modulates fc epsilon RII/CD23 expression in these patients.

Methods: We evaluated the expression of IgE receptors fc epsilon RI, fc epsilon RII/CD23, and soluble CD23 (sCD23), and the activation state of peripheral blood monocytes (tumor necrosis factor alpha, interleukin (IL) 1-beta, transforming growth factor (TGF) beta expression) in the patients with severe asthma before and after 24 weeks of omalizumab treatment and in the healthy controls. Cytokine expression of monocytes in response to different stimulation (IL-4, IL-4 plus IgE, IL-4 plus IgE plus anti-IgE, and IL-4 plus IgE plus anti-IgE plus anti-CD23 for 72 hours) was determined by enzyme-linked immunosorbent assay.

Results: Treatment with omalizumab (for 24 weeks) improved disease control and pulmonary function (forced expiratory volume in the first second of expiration, 64.5 versus 74%; $p = 0.021$). Mean $\pm$ SE expression of fc epsilon RI on monocytes was higher in the patients with asthma versus the controls ($45.7 \pm 12.2\%$ versus $18.6 \pm 5.8\%$; $p = 0.04$) and was reduced after omalizumab treatment ($45.7 \pm 12.2\%$ versus $15.6 \pm 4.4\%$; $p = 0.027$). Mean $\pm$ SE TGF-beta levels in supernatants from monocytes were reduced in the patients treated with omalizumab (211 ± 6 pg/mL versus 184 ± 9 pg/mL; $p = 0.036$).

Conclusion: Modulation of the low affinity IgE receptor CD23 in severe asthma is complex, and sCD23 may inversely reflect disease activity. Treatment with omalizumab was associated with reduced monocyte activation.

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Although only a minority of patients with asthma have severe disease, this group accounts for a large proportion of asthma-related hospital admissions, mortality, and costs.^{1–3} Omalizumab, a monoclonal humanized neutralizing anti-immunoglobulin E (IgE) antibody, has been demonstrated to improve symptoms and lung function and to reduce exacerbations in patients with moderate-to-severe atopic asthma and is recommended by Global Initiative for Asthma (GINA) guidelines for this indication.^{4–8}

IgE binds to the cell surface primarily *via* two receptors; a high affinity receptor, fcεRI, and a low affinity receptor, fcεRII (or CD23)^{9,10}; fcεRI is usually found as a tetramer ($\alpha\beta\gamma_2$) and is expressed primarily on mast cells and basophils but also on eosinophils, lymphocytes, monocytes, and dendritic cells.¹¹ IgE binding to

fcεRI on mast cells results in degranulation and release of multiple mediators, such as prostaglandins and histamine, which results in the “early asthmatic response.” CD23 belongs to the family of C-type animal lectin receptors and has an affinity 100–1000 times less than that of fcεRI.^{12–14}

After IgE binding, the receptor undergoes autocatalytic cleavage *via* disintegrin-metalloproteinase (ADAM), which results in the production of soluble protein fragments of variable molecular size and collectively referred to as soluble CD23 (sCD23).^{15–17} CD23 exists in two isomeric forms, CD23a and CD23b, that differ in their intracellular amino acid sequence and in the extracellular cleavage site.^{18,19} CD23a expression is constant (mainly found on B cells), whereas expression of CD23b is upregulated in response to interleukin (IL) 4 and IL-13, and is expressed primarily on monocytes, macrophages, eosinophils, and epithelial cells.^{20–23} CD23 is upregulated in allergic states. CD23 activation increases IL-4 expression in antigen-presenting cells, inhibits apoptosis of B lymphocytes, increases production of IgE by B cells, and increases expression of proinflammatory cytokines, including tumor necrosis factor (TNF) α , IL-1, and IL-6 from monocytes.^{24–26}

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It is not known whether the inflammatory effect of IgE in asthma is attributable solely to the interaction with $\text{Fc}\epsilon\text{RI}$ or whether the therapeutic efficacy of omalizumab is related solely to inhibiting this effect. In contrast to mast cells, monocytes and macrophages express relatively more CD23 than $\text{Fc}\epsilon\text{RI}$, and serum IgE expression correlates with CD23 expression on B lymphocytes and on monocytes and macrophages.^{12,19,26,27} Uptake of allergen-IgE complexes by B cells is mediated *via* CD23 and leads to activation of allergen-specific T cells. There is recent evidence that CD23 is expressed on naive B cells and its expression density correlates with the total IgE value and with a positive skin-prick test result.²⁸ IgE binding to CD23 is *via* a newly identified binding site on the stalk region of CD23, and this binding is blocked by omalizumab.²⁹

In this study, we evaluated whether the interaction between CD23 and IgE on peripheral blood monocytes is important in the chronic inflammation of asthma and whether the therapeutic effect of omalizumab is, in part, *via* attenuating this interaction.³⁰ We measured the expression of $\text{Fc}\epsilon\text{RI}$ and CD23 on blood monocytes from healthy controls and from patients with severe asthma before and after treatment with omalizumab for 24 weeks. We also evaluated the activation status of monocytes in patients with severe asthma as determined by expression of $\text{TNF-}\alpha$, $\text{IL-1}\beta$, and transforming growth factor (TGF) β before and after treatment with omalizumab.

METHODS

Subjects

Patients ages 18–75 years with severe uncontrolled asthma as defined by the GINA guidelines,⁷ who were eligible for treatment with omalizumab based on clinical indications were included in the study.^{3,31} Eligibility included patients in GINA step 5 with poorly controlled asthma, reversibility ($>12\%$ for forced expiratory volume in the first second of expiration [FEV_{1}]) positive skin-prick test results or radioallergosorbent tests, IgE levels of >30 U and <1500 U, two or more exacerbations that required systemic steroids in the preceding 12 months, and nonsmokers. The study was approved by the local ethics committee, and all the participants signed informed consent before enrollment. The participants received omalizumab for 24 weeks in addition to regular asthma medication with high-dose inhaled corticosteroids (ICS) and long-acting β -agonists.

Before initiating therapy, eligible patients performed spirometry with reversibility testing, completed an asthma questionnaire of disease control (the Juniper questionnaire), and a sample of 50 mL of venous heparinized blood was drawn. An interim clinical visit was performed at 16 weeks, and a final visit was performed after 24 weeks of treatment. The final visit included

repeated spirometry, blood tests, and the questionnaire. The decision as to whether to continue with omalizumab therapy at the end of the study was made based on clinical grounds and was unrelated to participation in the study. Expression of membrane-bound $\text{Fc}\epsilon\text{RI}$ and CD23 on peripheral blood monocytes, serum sCD23, and state of activation of monocytes as determined by expression of $\text{IL-1}\beta$ and $\text{TNF-}\alpha$ were measured in peripheral blood from healthy controls and from patients with severe asthma before and 24 weeks after initiation of omalizumab treatment.

Monocyte Isolation

For each patient, 50 mL of peripheral blood, was drawn into a heparinized syringe, mixed with buffer (phosphate-buffered saline [PBS] solution–EDTA 2 mM, pH 7.2) and separated by using Ficoll Hypaque (GE Healthcare, Little Chalfont, UK) and centrifugation. The mononuclear cell layer, which contains monocytes and lymphocytes, was carefully removed by using a plastic pipette and placed into a PBS–EDTA buffer solution. After repeated centrifugation to remove red blood cells and platelets, monocytes were mixed with CD-14 binding magnetic microbeads (MACS; Miltenyi Biotec, Bergisch Gladbach, Germany), and positive selection was performed by passing the cells over a magnetic column. The column was then washed three times with PBS–EDTA–bovine serum albumin buffer solution, and the cells were then separated from the column and used for additional experiments.

Fluorescence-Activated Cell Sorting Analysis

Freshly isolated and separated monocytes were counted and divided into aliquots of 0.5 million cells. Cell purity was evaluated by using fluorescein isothiocyanate labeled anti-CD14 (Miltenyi Biotec, Bergisch Gladbach, Germany), expression of membrane-bound CD23 and $\text{Fc}\epsilon\text{RI}$ were evaluated by using primary anti-CD23 and anti- $\text{Fc}\epsilon\text{RI}$ Phycoerythrin conjugated antibodies (eBioscience, San Diego, CA). Negative controls were performed in the absence of specific antibody.

Enzyme-Linked Immunosorbent Assay for $\text{TNF-}\alpha$, $\text{IL-1}\beta$, sCD23

Monocytes were plated in cell culture wells in Roswell Park Memorial Institute-containing penicillin, streptomycin, and glutamine. Basal expression was determined in supernatants from cells plated overnight (16–18 hours) without additional stimulation. To determine whether the behavior of monocytes in response to stimulation differs in controls and in the patients with asthma before and after omalizumab treatment, monocytes were cultured for 72 hours and

Table 1 Demographics and clinical characteristics of the patients with severe asthma

Patient No.	Age, y	M or F	% FEV ₁ After Rx	% FEV ₁ Before Rx	IgE, IU/L	Weight, kg	Oral Steroids	Dose, mg
1	53	F	85	NA	238	60	Yes	225*
2	30	M	75	100	928	69	Yes	375*
3	40	F	76	81	1178	55	No	375*
4	61	F	67	43	268	57	Yes	225*
5	69	M	59	64	651	80	No	375*
6	54	F	64	62	341	60	No	225*
7	63	M	57	43	1038	78	No	600*
8	42	M	37	NA	1475	72	No	600*
9	66	F	54	78	190	98	No	300#
10	60	M	54	82	338	90	No	300*
11	39	M	65	64	180	115	Yes	225*
12	45	M	79	77	143	82	Yes	300#
13	28	F	56	84	72	62	No	150#
14	30	M	47	NA	180	60	No	450#
15	18	M	118	120	1054	72	No	600*
16	20	M	59	63	523	80	No	450*
17	21	F	66	53	638	71	No	450*
18	49	F	31	71	226	63	No	450#
19	68	F	49	63	929	80	Yes	600*
20	72	M	43	42	894	84	No	600*

IgE = Immunoglobulin E; FEV₁ = forced expiratory volume in the first second of expiration; RX = treatment; NA = not available; M = Male; F = Female.

*Every 2 wk.

#Every 4 wk.

TNF- α , IL-1 β , sCD23 were measured in supernatants. The cells were stimulated as follows:

- With IL-4 (10 ng/mL)
- IL-4, followed by IgE (5 μ g/mL; Abcam, Cambridge, United Kingdom)
- IL-4 plus IgE plus anti-IgE, which is expected to increase cell activation by cross-linking membrane-bound IgE
- IL-4, followed by blocking anti-CD23 antibody and, thereafter, by IgE plus anti-IgE.

IL-4 (10 ng/mL) was added 24 hours after plating, IgE plus α -IgE (5 μ g/mL) 48 hours after plating, anti-CD23 (10 μ g/mL) 1 hour before IgE plus anti-IgE.

Clinical Evaluation

A standard asthma control questionnaire (Juniper questionnaire) was used to evaluate the clinical response to therapy.³¹ The questionnaire comprises six questions, each graded from 0 to 6. This questionnaire includes nighttime and morning waking symptoms, limitation of daily activities, the presence of shortness of breath and wheeze, and the use of reliever medication.

Statistical Analysis

The data were analyzed by using PRISM-4 software (GraphPad Software Inc., La Jolla, CA), and the values were expressed as median (interquartile range) or mean $\pm$ SE. The nonparametric Mann-Whitney test was used to compare receptor and cytokine expression in the patients and the controls. The Wilcoxon signed rank test was used to compare parameters before and after omalizumab. A *p* value of ≤ 0.05 was considered significant.

RESULTS

Patients

Twenty patients with severe asthma and 10 healthy controls were recruited for the study. Patient demographics, baseline FEV₁ (percentage predicted prebronchodilator), serum IgE levels, and the dose of omalizumab are listed in Table 1. Three patients discontinued omalizumab treatment before the 24-week follow-up visit; of these patients, one developed a rash after a single dose, one could not afford the cost of the treatment, and one withdrew consent. The average age of the patients was 46 years; 11 were men and 9 were women. Six of the patients were receiving maintenance low-dose oral corticosteroids.

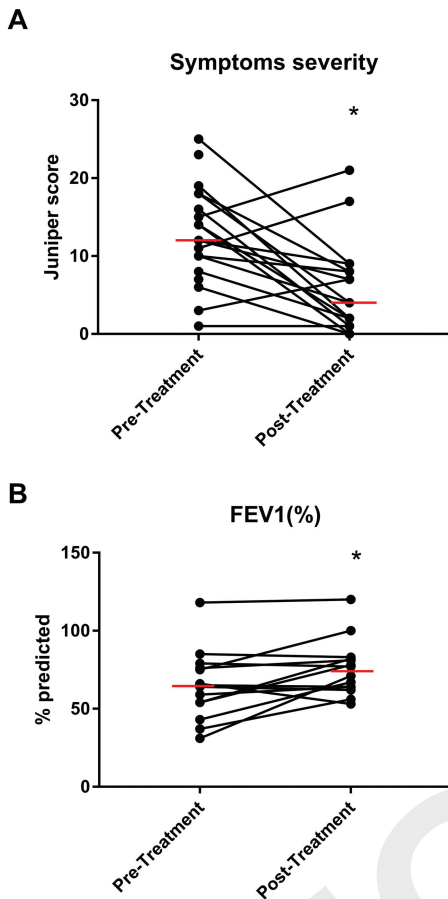


Figure 1. (A) An asthma control questionnaire performed before starting treatment and after 24 weeks of treatment showed a significant improvement in symptoms after treatment. * $p = 0.006$. (B) Percentage predicted for forced expiratory volume in the first second of expiration (FEV_1) in patients with asthma before and after 24 weeks of omalizumab therapy. # $p = 0.021$.

Clinical Response

There was significant improvement in asthma symptoms after treatment. Median value of 12 (25–75% 9–17) prior to treatment and median value of 4 (25–75% 1.5–8.5) after treatment ($p = 0.006$) (Fig. 1 A). A small but significant improvement in FEV_1 value was observed after omalizumab treatment: median 64.5% (25–75% 51–76.7) for pretreatment versus 74% (25–75% 63.5–82.3) (for post treatment) ($p = 0.021$) (Fig. 1 B).

Expression of $f\epsilon cRI$, Membrane-Bound CD23 ($f\epsilon cRII$) on Peripheral Blood Monocytes and sCD23

The mean $\pm$ SE percentage of $f\epsilon cRI$ positive cells was much higher in the patients with asthma than in the controls ($45.7 \pm 12.2\%$ versus $18.6 \pm 5.8\%$; $p = 0.04$) and was significantly reduced in the patients with asthma after treatment with omalizumab ($15.6 \pm 4.4\%$, $p = 0.027$, versus pretreatment) (Fig. 2 A). The mean $\pm$ SE percentage of monocytes expressing membrane-bound CD23 ($f\epsilon cRII$) was relatively low in all the

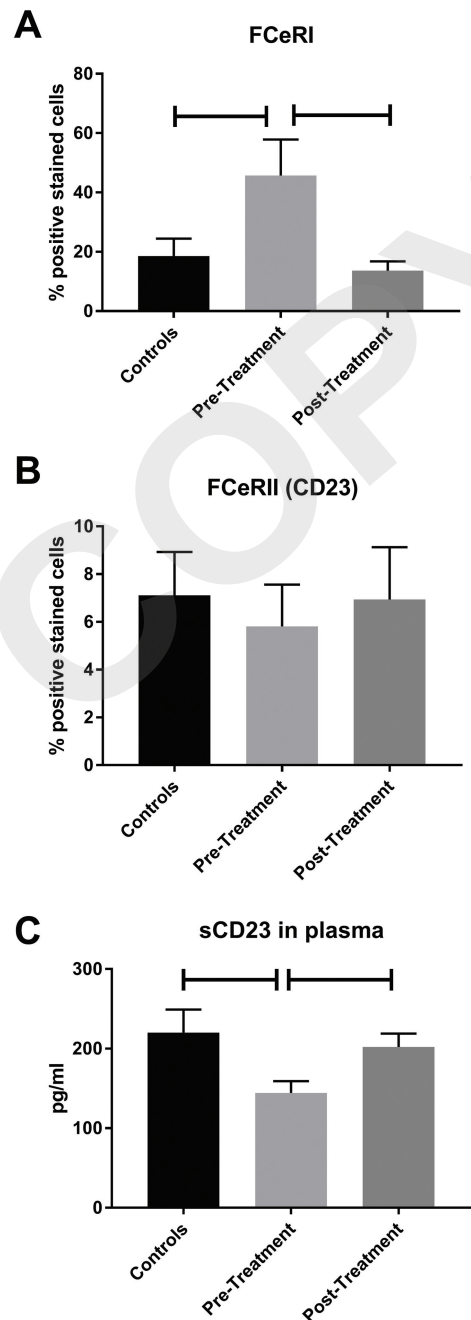


Figure 2. Expression of (A) high-affinity immunoglobulin E (IgE) receptor, $f\epsilon cRI$, and (B) membrane-bound CD23 ($f\epsilon cRII$) on peripheral blood monocytes from the control subjects (without asthma) ($n = 10$) and from the patients with severe asthma before ($n = 20$) and 24 weeks after initiating omalizumab treatment ($n = 17$). -controls versus the patients with asthma before treatment, $p = 0.02$; -patients with asthma before treatment versus after treatment, $p = 0.009$. (C) Soluble CD23 expression in the plasma of these groups. -controls versus patients with asthma before treatment, $p = 0.028$; -patients with asthma before versus after treatment, $p = 0.022$.

groups but was higher in the controls ($7.1 \pm 1.8\%$) than in the patients with asthma ($5.8 \pm 1.7\%$, not significant) and increased slightly after omalizumab therapy ($6.9 \pm$

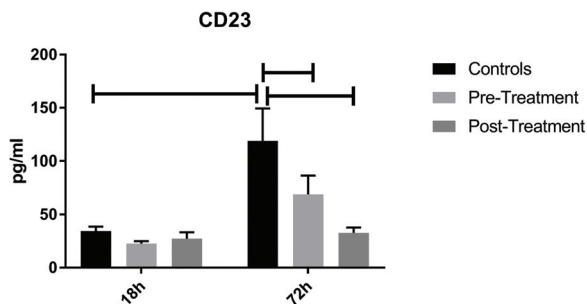


Figure 3. (A) Peripheral blood monocytes (0.5 million cells) from the controls and from the patients with asthma before and after omalizumab treatment were incubated in Roswell Park Memorial Institute medium for 18 hours or for 72 hours, and soluble CD23 was measured by enzyme-linked immunosorbent assay - $p = 0.02$.

2.2, not significant) (Fig. 2 B). A similar trend was observed for the mean $\pm$ SE sCD23 levels, with the highest levels observed in the controls (220 ± 29 pg/mL) compared with patients with asthma before treatment (144 ± 14 pg/mL; $p = 0.028$). After treatment, the mean $\pm$ SE sCD23 levels increased (202 ± 16 pg/mL [$p = 0.022$] versus pretreatment levels) (Fig. 2 C).

Modulation of Monocyte-Derived sCD23

Mean $\pm$ SE levels of sCD23 in supernatants from untreated monocytes of the healthy controls were higher compared with patients with asthma who were pretreated with omalizumab (34.4 ± 4 pg/mL versus 22.57 ± 2.2 pg/mL, $p = 0.02$, 18 hours; 118.9 ± 30 versus 68.9 ± 17.6 pg/mL 72 hours) (Fig. 3). At 72 hours, the mean $\pm$ SE levels of sCD23 were even lower in the patients with asthma after treatment with omalizumab (32.7 ± 5 pg/mL versus the controls with 118.9 ± 30 pg/mL, $p = 0.018$) (Fig. 3). Expression of CD23 was previously shown to be increased by IL-4 and IL-13. In this study, we found no significant difference in sCD23 levels in response to IL-4 with or without the addition of IgE and/or anti-IgE in any of the patient groups tested (data not shown).

Activation Status of Monocytes

To evaluate whether peripheral blood monocytes are activated in the patients with asthma, we measured the release of the inflammatory cytokines TNF- α and IL-1 β and of TGF- β from monocytes of the control, who did not have asthma, and from patients with severe asthma before and 24 weeks after treatment with omalizumab. For TGF- β , a small reduction was observed in the patients with asthma after omalizumab treatment (Fig. 4 A). The mean $\pm$ SE values of IL-1 β expression were significantly higher in the patients with asthma before treatment compared with the healthy controls (24.4 ± 8.1 pg/mL versus 6.08 ± 1.4 pg/mL; $p = 0.04$). A small but not significant reduction in IL-1 β levels was observed in

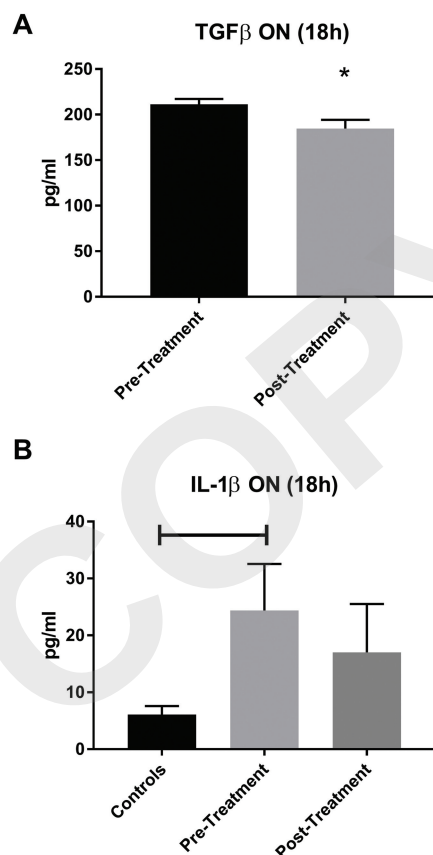


Figure 4. Expression of (A) Transforming growth factor (TGF) β in supernatants from peripheral blood monocytes (18 hours, 5×10^5 per well) from patients with severe asthma before and 24 weeks after initiating omalizumab treatment. $*p = 0.036$. (B) Expression of interleukin (IL) 1 β in supernatants of peripheral blood monocytes after 18 hours of incubation from the patients with severe asthma before and 24 weeks after initiating omalizumab treatment, $*p = 0.04$.

the asthma after omalizumab patient group (Fig. 4 B). No differences were observed for TNF- α in supernatants from monocytes in the control or asthma groups.

Mononuclear cells express both *fcεRI* and *fcεRII*. To evaluate whether peripheral blood monocyte activation may be influenced or mediated by the CD23 (*fcεRII*) receptor, we measured the release of TNF- α and IL-1 β from the monocytes of the controls without asthma and from the patients with severe asthma before and 24 weeks after treatment with omalizumab. For each group (the controls, the patients with asthma, the patients with asthma after omalizumab), cytokine release in supernatants was evaluated in unstimulated cells and after stimulation with IL-4 with or without IgE and anti-IgE with or without previous incubation with blocking antibodies for CD23.

For mononuclear cells from normal (without asthma) subjects, the mean $\pm$ SE expression of the TNF- α values was unchanged from baseline after the addition of IL-4 but was significantly increased after the addition of IL-4 together with IgE (565 ± 174 pg/mL versus

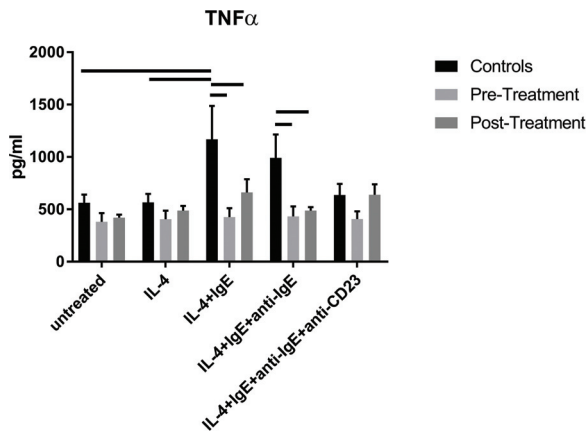


Figure 5. Tumor necrosis factor (TNF) α expression by monocytes of the healthy controls and the patients with asthma before and after omalizumab treatment. The cells were cultured in Roswell Park Memorial Institute medium in the presence of different stimuli (IL-4, IL-4 plus immunoglobulin E (IgE), IL-4 plus IgE plus anti-IgE, IL-4 plus IgE plus anti-IgE plus anti-CD23) for 72 hours. $p \leq 0.04$.

1169 $\pm$ 484 pg/mL; $p = 0.032$) and following IgE plus anti-IgE (991 $\pm$ 591 pg/mL, 431 $\pm$ 95 pg/mL; $p = 0.031$). Furthermore, this effect was attenuated in the presence of neutralizing anti-CD23 antibody (635 $\pm$ 263 pg/mL) (Fig. 5). In monocytes from patients with asthma, we found no significant difference in TNF- α expression in response to any of the given stimuli and no significant differences between monocyte TNF- α levels before and after omalizumab treatment (Fig. 5). Mean $\pm$ SE levels of TNF- α were significantly lower in stimulated monocytes from the patients with asthma versus the controls (IL-4 plus IgE, 425 $\pm$ 241 pg/mL versus 1169 $\pm$ 484 pg/mL; $p = 0.036$) and IL-4 plus IgE plus anti-IgE (432 $\pm$ 269 pg/mL versus 991 $\pm$ 591 pg/mL; $p = 0.04$) (Fig. 5).

DISCUSSION

We evaluated the expression of the high (*f ϵ RI*) and low (*f ϵ RII*, CD23) affinity receptors for IgE on peripheral blood monocytes and in plasma (sCD23) from the healthy controls and from the patients with severe asthma before and after 24 weeks of treatment with omalizumab. There was an improvement in asthma control and in lung function (FEV₁) of the patients treated with omalizumab. Although the high affinity receptor was elevated in the patients with asthma and was reduced after treatment, no such pattern was found for the low affinity receptor. Serum CD23 was lower in the patients with asthma and increased after therapy with omalizumab. In monocytes from the healthy controls but not from the subjects with severe asthma, expression of TNF- α increased in response to IL-4 and IgE, and this effect may have been mediated *via* the *f ϵ RII* receptor.

We observed a high expression of the *f ϵ RI* receptor in patients with severe asthma, and this was reduced in response to omalizumab therapy.⁵ We expected to ob-

serve a similar trend for *f ϵ RII* but found no significant differences between the controls and the patients with asthma before and after omalizumab. The low expression of CD23 on monocytes in our study was in contrast to previous publications, in which a high expression of this receptor on these cells is described^{13,14} and may be a consequence of treatment with oral or high-dose ICS that all the patients received before omalizumab treatment. If this is the case, then there may be a differential effect of ICS on the two IgE receptors. Evaluation of *f ϵ RII* expression on monocytes from the patients with asthma who did not receive ICS and the *ex vivo* effect of steroids on *f ϵ RII* and sCD23 expression would be informative.²⁰

In this study, sCD23 levels were in the reverse direction to that expected with the lowest measurements in the patients with severe asthma before omalizumab treatment and higher levels in healthy controls and after omalizumab treatment. The role and significance of sCD23 in general and the relationship between the membrane-bound and soluble forms of the receptor is unclear. Not infrequently, the cleaved soluble form of a membrane receptor serves an inhibitory function or reflects a reduction in function of the active membrane form of the receptor as is the case for the TNF receptor.³² Whether this is relevant to CD23 is unknown, but the possibility that sCD23 may inversely reflect disease activity or response to omalizumab treatment is intriguing.

We anticipated that the costimulation of monocytes *in vitro* with IL-4, together with extrinsic IgE with or without activating anti-IgE in the presence of blocking antibodies to the *f ϵ RII* receptor would enable us to evaluate whether these cells are activated *via* this receptor.^{33,34} TNF- α levels were increased in response to IL-4 plus IgE in monocytes from the control subjects only and were significantly higher than the levels in the patients with asthma and return to levels similar to baseline after addition of anti-CD23, which indicated that the increase in TNF levels in healthy subjects was mediated, in part, *via* *f ϵ RII* receptor activation with IgE.

It is not unlikely that the failure of monocytes from the patients with asthma to show the expected increase in response to stimulation is attributable to steroid medication. It is also possible that the culture conditions we used to evaluate monocyte activation (incubation for 72 hours) is accompanied by cell adhesion to the plastic wells and activation of cells at baseline. This may then interfere with the ability to evaluate further changes in cytokine expression in response to additional stimulation. For this study, we chose to examine monocytes, primarily because these cells were previously reported to express significant levels of CD23 relative to levels of *f ϵ RI*. Expression and regulation of *f ϵ RII* receptor is likely to be different in other cell types, such as in B cells and eosinophils, and similar experiments in these cells would certainly be of interest.^{14,30}

CONCLUSION

In addition to confirming the clinical efficacy of omalizumab, this study added new data on modulation of both membrane-bound and sCD23 in severe asthma before and after treatment with omalizumab. Analysis of our findings indicated that sCD23 levels may inversely reflect disease activity in patients with severe asthma. Furthermore, our findings indicated that the *f ϵ R11* receptor contributed monocyte activation in the control subjects, although the relevance of the *f ϵ R11* receptor in the patients with severe asthma was not clear.

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