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Effects of omalizumab on T lymphocyte function in inner-city children with asthma

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Capsule Summary

While omalizumab treatment of inner city children and adolescents with asthma results in improvement in clinical parameters, no change in peripheral blood T cell responses could be demonstrated. Thus, omalizumab appears not to affect T cell function.

Keywords

Omalizumab; T lymphocytes; Regulatory T cells; IL-13; Interferon γ; Cockroach allergy; Peripheral blood mononuclear cells; Lymphocyte stimulation; RT-PCR

To the Editor

Several theories regarding the mechanisms by which omalizumab provides benefit in asthma are emerging. By attaching to the specific Fc portion of IgE that binds to its high affinity receptor (FcεRI), omalizumab blocks binding of circulating IgE to the receptor on human basophils and mast cells. It also decreases free IgE levels, which leads to a marked down-regulation of FcεRI on basophils[1] and decreases basophil activation by allergens[2]. In addition, the spectrum of anti-inflammatory actions of anti-IgE treatment extends beyond IgE-bearing effector cells to include possible effects on antigen-presenting cells, eosinophils, T regulatory lymphocytes and Th2 cytokines[3].

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Studies in murine models of asthma have demonstrated that anti-IgE therapy reduces inflammatory cell accumulation in the lung. Moreover, Djukanovic and colleagues[4] found that treatment of asthmatic patients with omalizumab depleted IgE from airway tissues and reduced airway eosinophilia and IL-4 staining of bronchial biopsy cells. These findings, along with more recent studies demonstrating decreased levels of Th2 cytokines in omalizumab-treated individuals[3] , suggest that interruption of the allergic cascade initiated by IgE may modify the ensuing asthma-associated cellular inflammatory response.

The ICATA clinical study provided a unique opportunity to evaluate the effects of omalizumab therapy on peripheral blood T lymphocyte responses, regulatory T cell numbers, and IL-13 cytokine levels. The ICATA study, which was designed to evaluate the efficacy of omalizumab, as compared with placebo, when added to guidelines-based therapy in 419 inner-city children, adolescents and young adults with persistent asthma, found that omalizumab treatment significantly reduced the number of days with asthma symptoms as well as the proportion of participants who had one or more asthma exacerbations[5] .

Because T-cell-associated mechanisms may be at least partially responsible for the clinical effects demonstrated by omalizumab, we sought to evaluate cockroach-specific cell responses in a subgroup of the ICATA population using a whole peripheral blood mononuclear cell assay. Thus, our major goal was to determine whether or not this technique, one that was feasible to perform at more than one clinical site, could be used to detect cockroach-specific T cell cytokine changes (i.e., increased IFN-γ and decreased IL-13 production) after treatment with omalizumab. A secondary goal was to determine if T regulatory cell numbers would be increased by omalizumab treatment. Mechanistic data was obtained on 30 children in the placebo group and 31 children in the intervention group from two participating sites. For reporting purposes, data from cockroach-sensitive (CR sensitive) subjects will be used, a total of 41 subjects (19 and 22 children in the placebo and intervention groups respectively, see Table E1 in the Online Repository). These children did not differ with respect to mean age (10.1 years of age, control group vs. 10.9 years of age, intervention group), gender (52.6% male, control group vs. 68.2%, intervention group), race (89.5% Black, control group vs. 77.3%, Black, intervention group) or any of the other parameters that were evaluated.

For the cockroach-allergen-stimulated T lymphocyte studies, PBMCs were stimulated in the presence of three different concentrations of cockroach allergen at three different assay time points (see supplemental material for experimental procedure) and mRNA expression for IL-13 and IFN-γ was measured. As shown in Table 1, there was no difference between the two groups in the mean mRNA copies for either of these two cytokines at any concentration of cockroach allergen at any time point. This absence of effect also was seen when CR sensitive and CR insensitive subjects were combined and analyzed separately (data not shown).

Over the last decade, there has been accumulating data demonstrating an important role for regulatory T cells in allergen immunotherapy. More recently, through better characterization methods, regulatory CD4+ T cells have been shown to have increased surface expression of CD25+, increased expression of the intracellular transcription factor FoxP3 and reduced

expression of CD127. While these cells compose a very small fraction of the CD4+ T cell population, they can be identified in vivo and their proportions and absolute numbers have been shown to increase during allergen immunotherapy[6]. Despite the mounting evidence regarding their importance in allergen immunotherapy, the role of T regulatory cells in omalizumab therapy is not known. Thus, to explore this question in our ICATA subgroup, we evaluated the total number of these cells before and after treatment with omalizumab or placebo. At baseline, we found no difference in the absolute number or the percentage of CD3+CD4+CD25+CD127lo FoxP3+ cells between the control and intervention groups; moreover, we saw no difference in either the absolute numbers or the percentage of these cells in the blood in either the omalizumab or placebo treatment groups at week 60 (Table 1: absolute numbers: control 27 (18) vs intervention 21 (14); percentage: control 3.2 (1.6) vs intervention 2.6 (1.0).

Finally, we sought to determine if baseline IL-13 mRNA expression and T regulatory cell numbers/percentages are related to the efficacy of omalizumab therapy. As shown in Table 2, when baseline regulatory T cell numbers/percentages and IL-13 mRNA levels were dichotomized into “low” versus “high” groups, based on the median, neither of these biomarkers were predictive of maximum symptom days, composite asthma severity index or occurrence of exacerbations in the omalizumab-treated subgroup over the course of the study. Similar findings were seen when CR sensitive and CR insensitive subjects were combined and analyzed separately (data not shown).

In summary, while clinical improvement was seen, we were unable to demonstrate changes in cockroach-stimulated cytokine responses in PBMC or regulatory T cell numbers during treatment of inner city children and adolescents with omalizumab. The absence of an effect on cytokine responses could mean that omalizumab had no effect on cockroach-allergen-specific T cell responses in the ICATA study population. However, it is more likely that this PBMC assay was not sensitive enough to detect such differences. In support of this notion, a recent study by Oseroff et al. [7] demonstrated that, while IL-5 and IFN-γ responses can be and are elicited from cockroach-stimulated T cells from cockroach-allergic donors, these responses require in vitro expansion of Bla-g-specific T cells due to the low precursor frequency of these cells in the peripheral blood. Regarding our inability to detect a change in regulatory T cell numbers, this result may indicate that T regulatory cells are not generated during omalizumab therapy. However, it also is possible that these cells may have been absent in the peripheral blood but present in the target organ, as has been demonstrated by others in allergic rhinitis models[8].

While we were unable to demonstrate an effect of omalizumab on peripheral blood T cell responses in the ICATA study, children treated with this agent demonstrated marked improvement in asthma symptoms and exacerbation occurrence. Thus, our mechanistic studies suggest that the efficacy of omalizumab may not be dependent upon its effects on T cells, but rather to its effects on alternative cell types, possibly mast cells, basophils and/or dendritic cells. However, before it can be said definitively that omalizumab does not affect T cell function, more sensitive and specificT cell assays and/or studies that evaluate T cell function in the lung will need to be performed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Results of T-Cell Studies at Week 60 (ITT & CR-sensitive) *

		Control Mean (SD)	Intervention Mean (SD)	p value #
Lymphocyte Cytokine Expression (mRNA copies)		N=15	N=16	
(IL-13/UBE)	CR3, 48 hr	0.009 (0.011)	0.010 (0.002)	0.24 1
	CR10, 24hr	0.008 (0.007)	0.004 (0.002)	0.32 1
	CR10, 48 hr	0.009 (0.009)	0.020 (0.024)	0.23 1
	CR10, 72 hr	0.012 (0.009)	0.014 (0.013)	1 1
	CR30, 24hr	0.009 (0.008)	0.007 (0.004)	0.86 1
	CR30, 48 hr	0.012 (0.012)	0.010 (0.008)	0.54 1
	CR30, 72 hr	0.012 (0.008)	0.016 (0.013)	0.67 1
	mABS, 24 hr	0.083 (0.068)	0.044 (0.028)	
(IFNγ/UBE)	CR3, 48 hr	0.14 (0.15)	0.18 (0.19)	0.69 1
	CR10, 24hr	0.32 (0.65)	0.31 (0.45)	0.37 1
	CR10, 48 hr	0.21 (0.29)	0.26 (0.43)	0.77 1
	CR10, 72 hr	0.19 (0.19)	0.14 (0.08)	1 1
	CR30, 24hr	0.33 (0.60)	0.28 (0.47)	0.72 1
	CR30, 48 hr	0.19 (0.25)	0.13 (0.22)	0.56 1
	CR30, 72 hr	0.13 (0.10)	0.09 (0.08)	0.25 1
	mABS, 24 hr	2.12 (1.53)	4.05 (4.25)	
Treg Cells		N=15	N=17	
CD3+CD4+CD25+CD127-FoxP3+ (Abs cells/μL)		27 (18)	21 (14)	0.26 1
CD3+CD4+CD25+CD127-FoxP3+ (%)		3.2 (1.6)	2.6 (1.0)	0.24 1
CD3+CD4+CD25+CD127-FoxP3+ of CD3+CD4+ (%)		6.9 (2.7)	5.9 (1.7)	0.29 1
CD3+CD4+CD25+ FoxP3+ (Abs cells/μL)		31 (19)	26 (16)	0.42 1
CD3+CD4+CD25+ FoxP3+ (%)		3.7 (1.6)	3.2 (1.3)	0.42 1
CD3+CD4+CD25+ FoxP3+ of CD3+CD4+ (%)		8.0 (2.6)	7.5 (2.1)	0.54 1

* Study participants from the Chicago and Cleveland sites.

¶ Cockroach sensitive is defined as a German Roach Wheal size of ≤3mm from the Allergen Skin Test.

Similar results were found for CR-sensitive and CR-insensitive subjects combined as well as in the Per-Protocol Population.

1 Wilcoxon Test

Table 2

Level of Omalizumab Efficacy on Asthma Severity Indicators

		Maximum Symptom Days*			Asthma Burden Index§			Any Exacerbations¶		
Subgroup (Biomarker @ Baseline)	**N**	**Effect**	**P**	**p-int**	**Effect**	**P**	**p-int**	**OR (95% CI)**	**P**	**p-int**
log(IL-13/UBE) @ CR30, 72hr										
≤ −1.5	18	−0.27	0.78	0.90	0.71	0.54	0.37	2.09 (0.43 - 10.2)	0.35	0.83
> −1.5	16	−0.10	0.91		−0.69	0.51		1.65(0.34-8.06)	0.52	
CD3+CD4+CD25+CD127-FoxP3+ (Abs cells /μL)										
≥ 25	31	−0.59	0.39	0.76	−0.48	0.54	0.98	0.55(0.18-1.73)	0.30	0.47
> 25	27	−0.30	0.66		−0.51	0.52		1.02(0.31-3.35)	0.98	
CD3+CD4+CD25+FoxP3+ (Abs cells/μL)										
≥ 28	27	−0.61	0.37	0.95	−0.85	0.27	0.65	0.69(0.22-2.17)	0.52	0.85
> 28	31	−0.55	0.42		−0.35	0.66		0.81(0.24-2.76)	0.74	

*The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.

§The Composite Asthma Severity Index (CASI) quantifies disease severity by taking into account impairment, risk and the amount of medication needed to maintain control. CASI scores include 5 domains: day symptoms and albuterol use, night symptoms and albuterol use, controller treatment, lung function measures, and exacerbations.

¶An exacerbation was defined as a prednisone burst (a minimum of 20 mg per day of prednisone, or the equivalent, taken for any 3 of 5 consecutive days) or a hospitalization.