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Anti-IgE therapy results in decreased myeloid dendritic cells in asthmatic airways

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Capsule Summary

Anti-IgE treatment of intermittent to mild-persistent asthma in a cohort of seven volunteers resulted in improved allergen-induced airway hyperreactivity and a significant reduction in the number of airway myeloid dendritic cells.

Keywords

Anti-IgE treatment; Allergic Asthma; Dendritic cells (DCs); Myeloid DCs (mDCs); Plasmacytoid DCs (pDCs)

To the Editor:

Immunotherapy targeting immunoglobulin E (IgE) reduces aero-allergic hypersensivity and is an FDA-approved treatment option for moderate to severe allergic asthma.[1] Treatment with anti-IgE (Omalizumab, Genentech Inc. and Novartis Corp.) results in a marked reduction in the airway inflammation of asthmatics with a significant decrease in bronchial eosinophils and both CD4+ and CD8+ T cells.[2] The primary antigen presenting cells in the lung, dendritic cells (DCs) play a critical role in airway inflammation in asthma, because they constantly sample

inhaled allergens/antigens and stimulate antigen-specific T cells.[3, 4] It is known that pulmonary inflammation results in an increase in the number of lung DCs.[5] Accordingly, steroid therapy of asthmatics that diminished the airway inflammation resulted in a reduction in airway DC numbers.[6] Thus, we hypothesized that anti-IgE treatment in asthma volunteers might result in reduced airway DC numbers and decrease their maturation phenotype.

The study included seven intermittent to mild-persistent asthmatics undergoing anti-IgE treatment. Omalizumab (anti-IgE) was administered subcutaneously over 12 wks, based on body weight and serum IgE levels (for details see online repository). All 7 subjects (2 males and 5 females, mean age 30yrs) had positive methacholine challenges and positive allergen skin tests described in detail elsewhere.[7] Allergen PC_{20} values (provocative concentration causing 20% reduction in FEV_1 values) were determined both before and after 12 wks of anti-IgE treatment. All subjects showed a significant increase in PC_{20} values from before to after anti-IgE treatment (p-value = 0.03) except one subject who failed to respond to the tested allergen even before anti-IgE treatment (see Figure 1). Thus, there was an improvement in allergen-specific airway hyperreactivity (AHR) in 6 of 7 subjects following anti-IgE treatment, a finding similar to a previous report.[8]

BALF and bronchial biopsy samples obtained at 2 wks before therapy, immediately after 12 wks of therapy and 2 months post-therapy were evaluated for inflammatory cell numbers. Subjects were lavaged using 300ml of saline with a mean BALF recovery of 197.5 ml (range 72-256 ml). There was no significant change in the BALF cells. The biopsy samples were also analyzed semi-quantitatively for intraepithelial and subepithelial inflammatory cell and mucus cell numbers by a pathologist blinded to the timing of the samples. Similar to BALF cellularity, there was no significant change in mucus cells, intraepithelial or subepithelial mononuclear cells, eosinophils or neutrophils.

We next examined DCs in bronchial biopsies following multicolor immunostaining and multispectral confocal imaging techniques (see details on online repository). Airway myeloid DCs (mDCs or conventional DCs) and plasmacytoid DCs (pDCs) were identified, localized and enumerated in these biopsies. For enumeration of DC subsets, the lineage negative (Lin-) cells (cells that did not express specific T cell, B cell, monocyte, neutrophil or NK markers) that expressed the β_2-integrin CD11c and HLA-DR were identified as mDCs; whereas Lin- cells expressing the IL3-receptor α-subunit CD123 and HLA-DR were identified as pDCs.[3, 4] mDCs were observed in both intraepithelial and subepithelial mucosa, whereas all of the pDCs observed were in the subepithelial region (Figure E1). As depicted in Figure 2A, there was a highly significant (p-value=0.0046) decrease in the number of mDCs immediately after anti-IgE treatment, that persisted for 2 months post-treatment (p-value=0.0205). The average number of mDCs in pre-treatment biopsies was 126/mm^2 (range, 28-246) compared to 38/mm^2 (range, 10-66) immediately after 12 wks of treatment and 49/mm^2 (range, 10-151) 2 months post-treatment. However, the number of pDCs were not significantly changed at either the end of therapy or at 2 months post-therapy (Figure 2B). The average number of pDCs/mm^2 in the biopsies was 12/mm^2 (range, 0-38) pre-treatment compared to 31/mm^2 (range, 0-104) immediately after treatment and 43/mm^2 (range, 10-85) 2 months post-treatment. It is possible that the trend towards an increase in pDCs could have become significant with additional numbers of study subjects.

The surface expression of selected function-associated markers on DCs was also analyzed, but there were no significant changes in the percentages of mDCs and pDCs that expressed CD80, CD83 and CD1a, and CD80, CD83 and BDCA2, respectively (Figure E2). The biopsies were also analyzed for changes in CD4+, CD8+ T cells and T regulatory cells, but unlike a previous report,[2] we found no effect on the bronchial T cells (Figure E3) following anti-IgE therapy. We believe that this inconsistency could be explained by differences in the severity of asthma

in the study subjects. However, we observed a trend toward reduction in the CD4+ T cells, and it is also possible that samples from additional volunteers would have shown a significant decrease.

In summary, in this study of 7 volunteers, we demonstrate that anti-IgE therapy in intermittent to mild persistent asthma resulted in a significant decrease in airway mDCs associated with improved PC_{20} values. Asthma-associated AHR likely results from chronic inflammation; and allergen-specific T cells play an important role in the maintenance of chronic inflammation.[9] DCs are essential for the initiation of primary T cell responses, and they are also very efficient in re-stimulating memory T cells. Thus, we speculate that the decrease in airway mDCs following anti-IgE treatment might contribute in the long term to reduced T cell activity and airway inflammation, and consequently to decreased AHR. We do not believe that the anti-IgE therapy directly reduced mDCs, but rather reduced activation of airway mast cells (due to a decrease in IgE binding to these important effector cells) is most likely the primary effect of therapy. Consistent with this idea, a separate study showed that the same subjects enrolled in this report had a marked reduction in the FcεRI-mediated release of Th2 cytokines and chemokines by peripheral blood basophils following anti-IgE treatment.[7] Thus, the diminished release of DC chemotactic chemokines resulting either directly or indirectly from less mast cell activation and secretion could be responsible for the decrease in airway mDC numbers. Strikingly, a decrease in the number of mDCs was detected although the number of other inflammatory cells did not change significantly, which suggests, in view of the clinical response in these patients, that mDC numbers might be a very sensitive indicator of modulation in tissue inflammation.

Acknowledgments

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Abbreviations

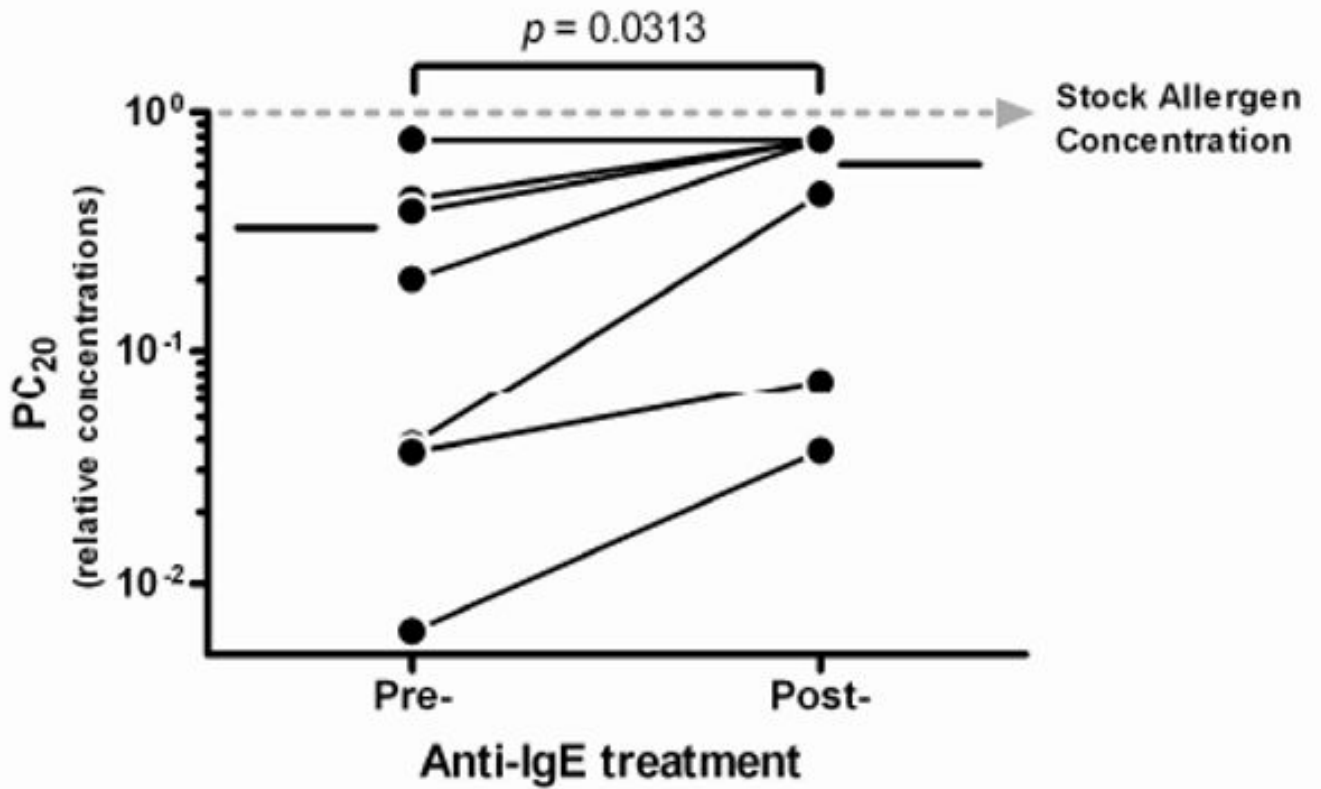|	
DCs	Dendritic cells
mDCs	myeloid DCs
pDCs	plasmacytoid DCs
IgE	immunoglobulin E
FEV_1	forced expiratory volume in 1 second
PC_{20}	provocative concentration causing 20% reduction in FEV_1 values from baseline

Figure 1. Effect of 12 weeks of anti-IgE treatment on the allergen-specific PC$_{20}$ values of asthma volunteers

PC$_{20}$ values or relative allergen concentrations at which the FEV1 values decreased by at least 20% from baseline were determined both before and after 12 wks of anti-IgE treatment. The mean PC$_{20}$ values are indicated on either side of time-points by solid horizontal lines.
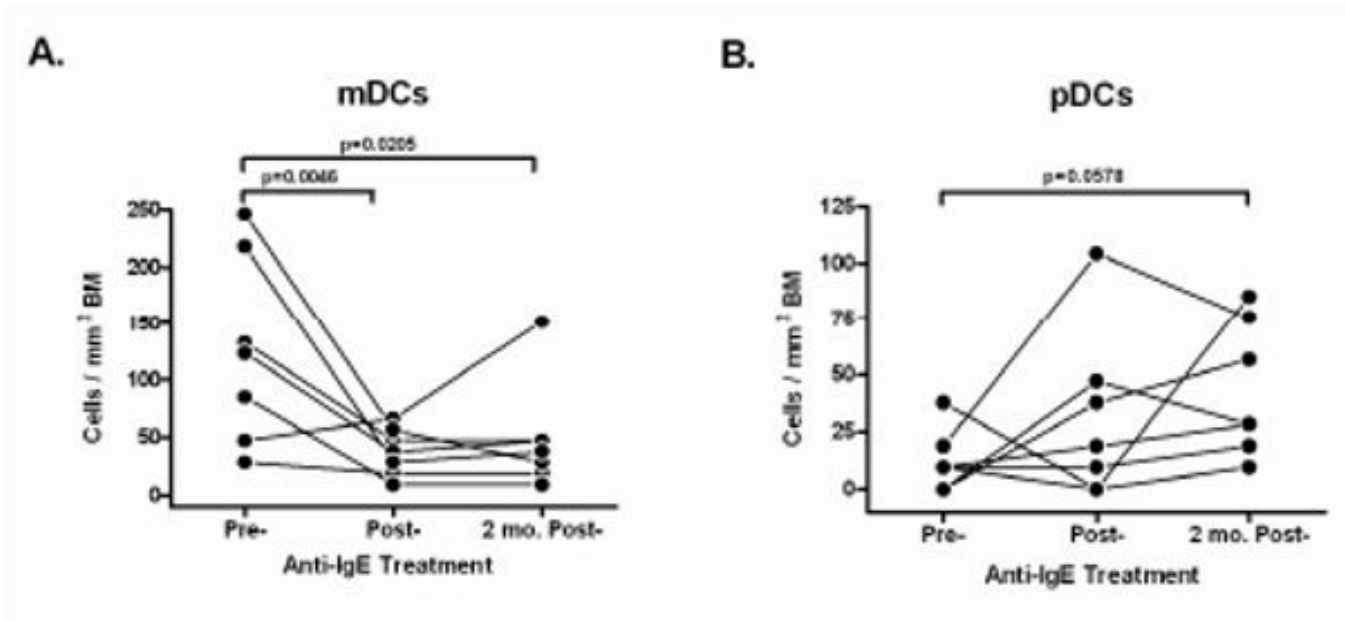
Figure 2. Effect of anti-IgE treatment on the numbers of mDCs and pDCs in asthmatic airways (N=7)
Numbers of mDCs (**A**) and pDCs (**B**) were determined by multispectral image analysis of airway biopsies by counting Lin-CD11c+HLA-DR+ cells and Lin-CD123+HLA-DR+ cells per mm^2, respectively from separate serial sections. The data from individual subjects is plotted as an average of 4 sections per time-point.