

2. Pohl-Koppe A, Burchett SK, Thiele EA, Hafler DA. Myelin basic protein reactive Th2 T cells are found in acute disseminated encephalomyelitis. *J Neuroimmunol* 1998;91:19-27.
3. Brocke S, Gaur A, Piercy C, Gautam A, Gijbels K, Fathman CG, et al. Induction of relapsing paralysis in experimental autoimmune encephalomyelitis by bacterial superantigen. *Nature* 1993;365:642-4.
4. Schwarz S, Mohr A, Knauth M, Wildermann B, Storch-Hagenlocher B. Acute disseminated encephalomyelitis: A follow-up study of 40 adult patients. *Neurology* 2001;56:1313-8.
5. Pette M, Fujita K, Wilkinson D, Altmann DM, Trowsdale J, Giegerich G, et al. Myelin autoreactivity in multiple sclerosis: recognition of myelin basic protein in the context of HLA-DR2 products by T lymphocytes of multiple sclerosis patients and healthy donors. *Proc Natl Acad Sci U S A* 1990;87:7968-72.
6. Martin R, Jaraquemada D, Flerlage M, Richert J, Whitaker J, Long EO, et al. Fine specificity and HLA restriction of myelin basic protein-specific cytotoxic T cell lines from multiple sclerosis patients and healthy individuals. *J Immunol* 1990;145:540-8.
7. Wucherpfennig KW, Sette A, Southwood S, Oseroff C, Matsui M, Strominger JL, et al. Structural requirements for binding of an immunodominant myelin basic protein peptide to DR2 isotypes and its recognition by human T cell clones. *J Exp Med* 1994;179:279-90.
8. Wucherpfennig KW, Catz I, Hausmann S, Strominger JL, Steinman L, Warren KG. Recognition of the immunodominant myelin basic protein peptide by autoantibodies and HLA-DR2 restricted T cell clones from multiple sclerosis patients: identity of key contact residues in the B cell and T cell epitopes. *J Clin Invest* 1997;100:1114-22.
9. Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. *Cell* 1995;80:695-705.
10. Gautam AM, Lock CB, Smilek DE, Pearson CI, Steinman L, McDevitt HO. Minimum structural requirements for peptide presentation by major histocompatibility complex class II molecules: implications in induction of autoimmunity. *Proc Natl Acad Sci U S A* 1994;91:767-71.

doi:10.1067/mai.2002.52

Treatment with omalizumab normalizes the number of myeloid dendritic cells during the grass pollen season

To the Editor:

Humanized anti-IgE antibodies are safe and effective in treating patients with allergic rhinitis and asthma.¹ Therapeutic anti-IgE antibodies such as omalizumab have a unique binding specificity in that they bind to soluble IgE and to membrane-bound IgE on IgE-expressing B cells but not to IgE already bound by high-affinity receptors (FcεRI) on mast cells and basophils or by low-affinity IgE Fc receptors (FcεRII) on other cell types.² In addition to neutralizing free IgE and inhibiting IgE production by B cells,³ omalizumab might have additional immunomodulating effects on antigen-presenting cells.⁴ Recent research indicates that dendritic cells (DCs) are specialized for antigen uptake, processing, and presentation to T cells. Two subsets of DCs were identified in the blood: CD11⁺ myeloid DCs and CD123⁺ plasmacytoid DCs. Each represented a small fraction (0.3%) of mononuclear cells, and both subtypes differ in origin, in the route of activation, and in immunologic activity.⁵ A flow cytometric assay was designed to detect the 2 different subsets of peripheral blood dendritic cells.⁶ In this report, this assay was used to determine the frequency of DC subpopulations in children and adolescents treated with omalizumab.

Forty-nine patients were enrolled in this substudy. They were treated at 2 centers (Bochum and Wesel)

located in the western region of Germany as part of a phase IIIb, multicenter, randomized, double-blind, placebo-controlled, multiple-dose, parallel-group rhinitis study investigating the safety and efficacy of subcutaneously administered omalizumab in children and adolescents with seasonal allergic rhinitis (SAR). The whole study population consisted of 221 children and adolescents (6 to 17 years of age), each having a clinical history of birch pollen-induced and grass pollen-induced SAR within the previous 2 years. Signed informed consent was obtained from all subjects and their guardians, and the study design was approved by the ethics committees of the participating centers. The details of the core study are described elsewhere.⁷

Four treatment arms used omalizumab and specific immunotherapy (SIT): SIT/birch + omalizumab; SIT/birch + placebo; SIT/grass + omalizumab; and SIT/grass + placebo. SIT for birch or for grass (ALK-Scherax/Abello, Berlin, Germany) was administered with increasing doses with 12 weekly injections.⁷ Thereafter, patients were switched to 5 maintenance injections of SIT in a 4-week interval; placebo or omalizumab was added to the SIT for 24 weeks. Omalizumab was administered on the basis of body weight and serum total IgE, providing a dose of at least 0.016 mg/kg per IU/mL of IgE every 4 weeks.

During the birch season (>10 grains/m³ per 24 hours; April 3 to May 1) and the grass season (> 5 grains/m³ per 24 hours; May 11 to June 23), blood was obtained and stained for DCs. The respective mean cumulative doses at the time of blood collection during the relevant pollen season did not differ between patients treated with omalizumab and patients given placebo (SIT birch, 494630 versus 496335 SQ units; SIT grass, 614722 versus 634461 SQ units). Daily symptom severity scores (eyes and nose) and rescue medication usage (for definitions, see Kuehr et al⁷) were assessed during the pollen seasons.

Staining procedures were performed as follows: 100 μL of whole blood was incubated with 20 μL of the lineage cocktail fluorescein isothiocyanate, 10 μL anti-human leukocyte antigen D-related (HLA-DR) peridinin chlorophyll protein (PerCP), and either 5 μL CD11c PE, 5 μL CD123 PE, or the appropriate isotype controls (all from Becton Dickinson, Heidelberg, Germany). Measurements were performed on a FACScan flow cytometer (Becton Dickinson) equipped with a Power Macintosh G3 computer and CellQuest software. DCs were identified as showing no labeling for the lineage cocktail and strong labeling for HLA-DR. Through the use of 3-color analysis, the proportion of strongly CD123-labeled plasmacytoid cells and of CD11c⁺ myeloid cells among DCs was determined. The absolute number of blood DCs was calculated on the basis of the percentage of DCs and the absolute number of mononuclear cells, as determined by the blood count.⁶

The results are shown in Fig 1. DC numbers did not differ between patients with SIT birch and patients with SIT grass, and there was no difference between placebo-treated and omalizumab-treated patients in the birch season. Indeed, DC numbers in healthy age-matched control sub-

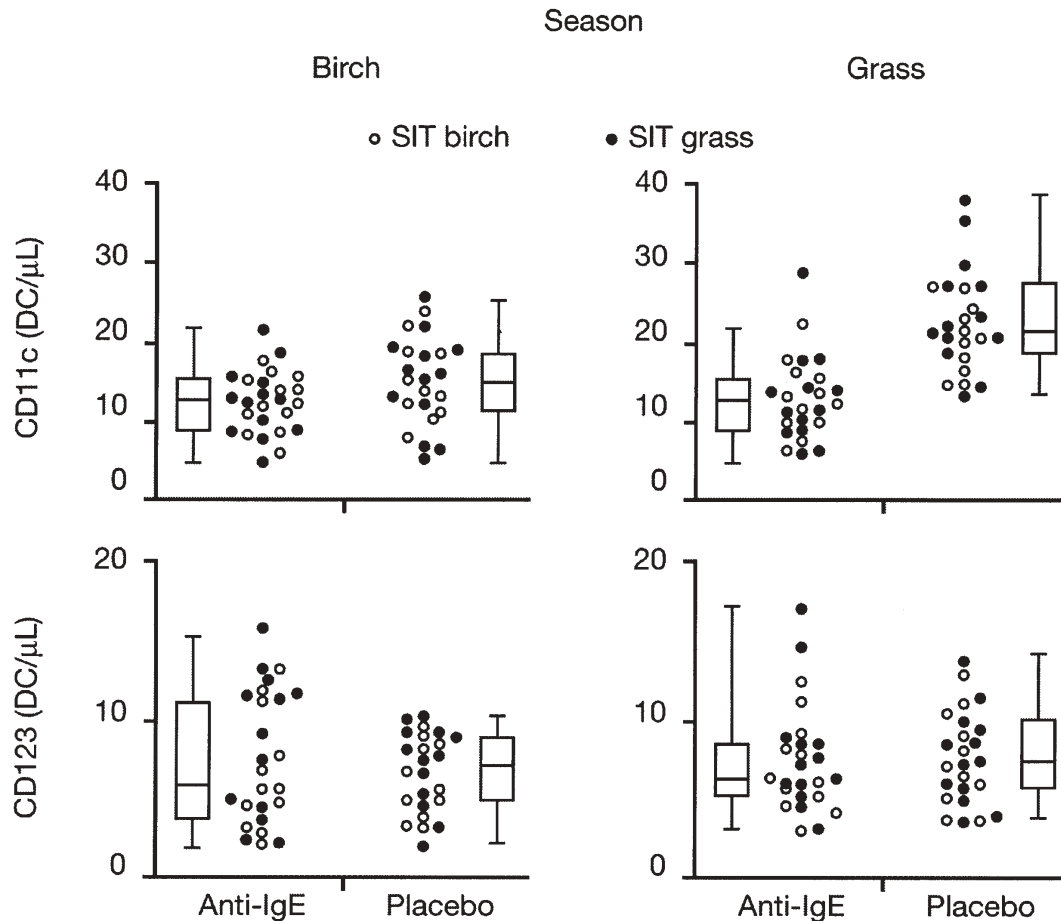


FIG 1. Myeloid DCs are increased in peripheral blood of placebo-treated patients with SAR during grass pollen season but not during birch pollen season. DC numbers in peripheral blood were calculated from placebo-treated and anti-IgE-treated subjects with SAR during birch and grass pollen seasons. There was no difference between patients treated in parallel with SIT-birch (*open circles*) and patients treated in parallel with SIT-grass (*closed circles*).

TABLE I. Characteristics of the study population

	Anti-IgE	Placebo	P value*
Background characteristics			
n (female/male)	16/9	8/16	.0465
Age (y)	12.3 (7.5–17.3)	12.9 (6.7–17.0)	.9884
SAR Duration (y)	6.25 (3.00–9.25)	6.52 (2.10–14.0)	.3416
Total IgE (kU/L)	300 (45.0–809)	333 (31.6–800)	.4407
Specific IgE† to birch	10.80 (0.49–125)	8.43 (0.44–125)	.9762
Specific IgE† to grass	43.9 (0.91–125)	88.7 (2.68–125)	.1100
Treatment			
SIT birch/SIT grass	12/13	11/13	.8792
Mononuclear cells (per μ L)			
Birch season	3100 (1638–5220)	3323 (1625–4565)	.6801
Grass season	3034 (1408–5213)	3149 (2213–4450)	.6782
Severity score			
Birch season	0.21 (0.00–2.03)	0.46 (0.00–4.61)	.5944
Grass season	0.66 (0.00–2.34)	1.51 (0.08–6.00)	.0110

SIT, Specific immunotherapy; SAR, seasonal allergic rhinitis.

Data are presented as median (range) values.

*Data were analyzed by Student *t* test for continuous variables and by Fisher exact test for discrete values.

†Specific IgE values >100 were set to 125; values <.35 were set to 0.

jects determined before the birch season⁶ (CD11c: median, 14.5/ μ L; range, 4.5 to 10.6/ μ L and CD123: median, 7.1/ μ L; range 3.8 to 12.3/ μ L) were in a range comparable to DC numbers of patients during the birch season in this study. Likewise, there was no difference in the numbers of CD123⁺ plasmacytoid DCs between placebo-treated and omalizumab-treated patients. However, we found considerably higher numbers (median, 21.2/ μ L; range, 13.5 to 38.2/ μ L) of CD11c⁺ myeloid DCs in the peripheral blood of placebo-treated patients than in that of omalizumab-treated patients (median, 12.4/ μ L; range, 6.0 to 29.1/ μ L) during the grass season. By ANOVA, the difference in numbers of DCs was significant ($P = .0137$), taking into account the differences in sex and the levels of specific IgE to grass pollen between the 2 groups (Table I). This increase was paralleled by a dramatic increase in the severity score (1.51 for the placebo group versus 0.66 for the omalizumab group; $P = .0110$).

There are several possible explanations for this relation. Katoh et al⁸ recently identified a new role for Fc ϵ RI on antigen-presenting cells in which Fc ϵ RI is involved in the regulation of apoptosis in monocytes. Monocytes have a limited life span, and their homeostasis is regulated by programmed cell death in vivo. Fc ϵ RI ligation on monocytes prevents apoptosis.⁸ The same mechanism might apply to myeloid DCs, which arise from monocytes. Conversely, the differentiation of monocytes into myeloid dendritic cells requires GM-CSF and IL-4.⁹ IL-4 is secreted by T cells as well as by mast cells. Nasal mast cells from patients with allergic rhinitis express high levels of the Fc ϵ RI and IL-4.¹⁰ Therefore, treatment with omalizumab might decrease the amount of mast cell-derived IL-4 during the pollen season and thus decrease the number of myeloid DCs. Because myeloid DCs (in the absence of proinflammatory cytokines) were shown to promote the differentiation of T_H2 cells,⁵ the observed effect of normalizing the number of myeloid DCs during the pollen season might provide an additional explanation for the clinical effects of anti-IgE treatment.

Tobias Feuchtinger, MD^a
Holger Bartz, MD^a

Andrea von Berg, MD^b
Frank Riedinger, PhD^c
Jens Brauburger, PhD^c
Stephan Stenglein, PhD^c
Ulrich Wahn, MD^d
Uwe Schauer, MD^a
^aUniversity Children's Hospital
Bochum
^bMarien-Hospital
Wesel
^cNovartis Pharma GmbH
Nuernberg
^dThe Department of Pediatric Pneumology and Immunology
Charité Humboldt University
Berlin
Germany

REFERENCES

1. Babu KS, Arshad SH, Holgate ST. Anti-IgE treatment: an update. *Allergy* 2001;56:1121-8.
2. Heusser C, Jardieu P. Therapeutic potential of anti-IgE antibodies. *Curr Opin Immunol* 1997;9:805-13.
3. Chang TW. The pharmacological basis of anti-IgE therapy. *Nat Biotechnol* 2000;18:157-62.
4. Coyle AJ, Wagner K, Bertrand C, Tsuyuki S, Bews J, Heusser C. Central role of immunoglobulin (Ig) E in the induction of lung eosinophil infiltration and T helper 2 cell cytokine production: inhibition by a non-anaphylactogenic anti-IgE antibody. *J Exp Med* 1996;183:1303-10.
5. Liu YJ, Kanzler H, Soumelis V, Gilliet M. Dendritic cell lineage, plasticity and cross-regulation. *Nat Immunol* 2001;2:585-9.
6. Teig N, Moses D, Gieseler S, Schauer U. Age-related changes in human blood dendritic cell subpopulations. *Scand J Immunol* 2002;55:453-7.
7. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002;109:274-80.
8. Katoh N, Kraft S, Wessendorf JH, Bieber T. The high-affinity IgE receptor (Fc ϵ sRI) blocks apoptosis in normal human monocytes. *J Clin Invest* 2000;105:183-90.
9. Sallusto F, Lanzavecchia A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. *J Exp Med* 1994;179:1109-18.
10. Pawankar R, Okuda M, Yssel H, Okumura K, Ra C. Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the Fc ϵ -sRI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997;99:1492-9.

doi:10.1067/mai.2003.56