

We do not know why the response to IgE cross-linking was greater in nonatopic individuals. Both atopic and nonatopic individuals expressed IgE on their cDCs, although expression was higher on cDCs from atopic subjects (20.4 ± 7.1 vs 12.3 ± 9.6 , mean fold mean fluorescence intensity (MFI) $\pm$ SEM, atopic vs nonatopic), similar to what has been reported.⁷ Perhaps anti-IgE treatment cross-linked a greater percentage of Fc ϵ RI on the cDCs from nonatopic individuals, translating into increased CCL28 production. Constitutive production of CCL28 was high in our cDC cultures, suggesting that factors other than IgE are important in baseline release of CCL28. Perhaps association of CCL28 and atopic status is a result of these other factors or cell types, especially in diseases like atopic dermatitis.⁸

This is the first study to demonstrate that human cDCs are a potent source of CCL28, and cross-linking cDC IgE increases CCL28 production by nearly 3-fold. Because our data show the Fc ϵ RI-CCL28 pathway is intact in human beings, it provides initial evidence that the virus-driven IFN α R-Fc ϵ RI-CCL28-IL-13 axis found in mice might also be operative in human beings.³ Unexpectedly, our data show that the level of CCL28 production is not a predictor of atopic status. Future studies will need to be performed to determine whether upstream or downstream events in this cascade impart a risk of atopic disease development.

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REFERENCES

1. Sigurs N. A cohort of children hospitalised with acute RSV bronchiolitis: impact on later respiratory disease. *Paediatr Respir Rev* 2002;3:177-83.
2. Stensballe LG, Simonsen JB, Thomsen SF, Larsen AM, Lysdal SH, Aaby P, et al. The causal direction in the association between respiratory syncytial virus hospitalization and asthma. *J Allergy Clin Immunol* 2009;123:131-7 e1.
3. Grayson MH, Cheung D, Rohlfing MM, Kitchens R, Spiegel DE, Tucker J, et al. Induction of high-affinity IgE receptor on lung dendritic cells during viral infection leads to mucous cell metaplasia. *J Exp Med* 2007;204:2759-69.
4. Lazarus NH, Kunkel EJ, Johnston B, Wilson E, Youngman KR, Butcher EC. A common mucosal chemokine (mucosae-associated epithelial chemokine/CCL28) selectively attracts IgA plasmablasts. *J Immunol* 2003;170:3799-805.
5. Wang W, Soto H, Oldham ER, Buchanan ME, Homey B, Catron D, et al. Identification of a novel chemokine (CCL28), which binds CCR10 (GPR2). *J Biol Chem* 2000;275:22313-23.
6. O'Gorman MT, Jatoi NA, Lane SJ, Mahon BP. IL-1 β and TNF- α induce increased expression of CCL28 by airway epithelial cells via an NF κ B-dependent pathway. *Cell Immunol* 2005;238:87-96.
7. Foster B, Metcalfe DD, Prussin C. Human dendritic cell 1 and dendritic cell 2 subsets express Fc ϵ RI: correlation with serum IgE and allergic asthma. *J Allergy Clin Immunol* 2003;112:1132-8.
8. Ezzat MH, Sallam MA, Shaheen KY. Serum mucosa-associated epithelial chemokine (MEC/CCL28) in atopic dermatitis: a specific marker for severity. *Int J Dermatol* 2009;48:822-9.

Sustained response to mepolizumab in refractory Churg-Strauss syndrome

To the Editor:

Churg-Strauss syndrome (CSS) is a primary small vessel vasculitis characterized by asthma, eosinophilia, multiorgan involvement (lung, peripheral nerves, heart, gastrointestinal tract, skin), and the possible presence of antineutrophil cytoplasmic antibodies (ANCA). Corticosteroids alone are the classic therapeutic regimen in the absence of poor prognostic factors, and use of cyclophosphamide is recommended for severe disease or corticosteroid-resistant cases. The other therapies tried in CSS (intravenous immunoglobulins, IFN- α , infliximab, rituximab) target the putative pathogenic pathways of ANCA-associated vasculitides without consideration for the hallmarks of CSS compared with other ANCA-associated vasculitides: important blood and tissue eosinophilia and lower prevalence of ANCA.¹

IL-5 is the main cytokine involved in eosinophil biology, and serum IL-5 levels may be increased in CSS. We report here for the first time the successful use of an anti-IL-5 humanized mAb (mepolizumab) in a patient with refractory CSS according to the American College of Rheumatology classification criteria.

A 28-year-old white woman with a long history of asthma presented in 1993 with marked hypereosinophilia ($26.7 \times 10^9/L$), interstitial pneumonia (60% eosinophils in bronchoalveolar lavage fluid), and myocarditis. She had no travel history or known helminthic or viral source of infection. At presentation, she did not have sinusitis, cutaneous, neurologic, or renal involvement. The serum IgE level was increased, at 1000 kIU/L ($N < 120$), and ANCAs were negative and remained so during the course of disease. She was initially treated with corticosteroids alone from 1993 to 1995. Many relapses (eosinophilia, asthma, and peripheral neuropathy) occurred between 1995 and 2007, requiring multiple therapeutic changes: methotrexate, IFN- α , cyclophosphamide, intravenous immunoglobulins, and azathioprine. In January 2007, while receiving inhaled fluticasone/salmeterol, oral prednisone (7 mg/d), azathioprine (50 mg/d), and intravenous immunoglobulins (60 g/mo) for the past 6 years, she experienced a relapse with eosinophilia ($18 \times 10^9/L$), severe asthma, interstitial pneumonia, and mononeuritis multiplex (involving left ulnar and peroneal nerves). Peak expiratory flow was 360 L/min, representing a 25% decrease from baseline. Creatinemia, FIP1L1-PDGFR α fusion gene, T-cell phenotype, and T-cell clonality were normal or negative. Serum eosinophil cationic protein (ECP) and IL-5 levels are shown in Table I. Electrocardiogram and echocardiography were normal. Cyclophosphamide and methylprednisolone pulses (1 g each) were started, and prednisone dosing was increased to 0.8 mg/kg. In April 2007, after 3 pulses of cyclophosphamide, asthma worsened (peak expiratory

TABLE I. Evolution of serum IL-5 and ECP levels 2 months before and 2 months and 8 months after initiation (mo) of monthly pulses of mepolizumab

	M-2	M+2	M+8
IL-5 (pg/mL)	19.89	66.2	60.1
ECP (μ g/L)	>200	27	12.3

IL-5, normal range <7.8 pg/mL; R&D Systems, Minneapolis, Minn. ECP, normal range <15 μ g/L; Phadia, Uppsala, Sweden. M, Month.

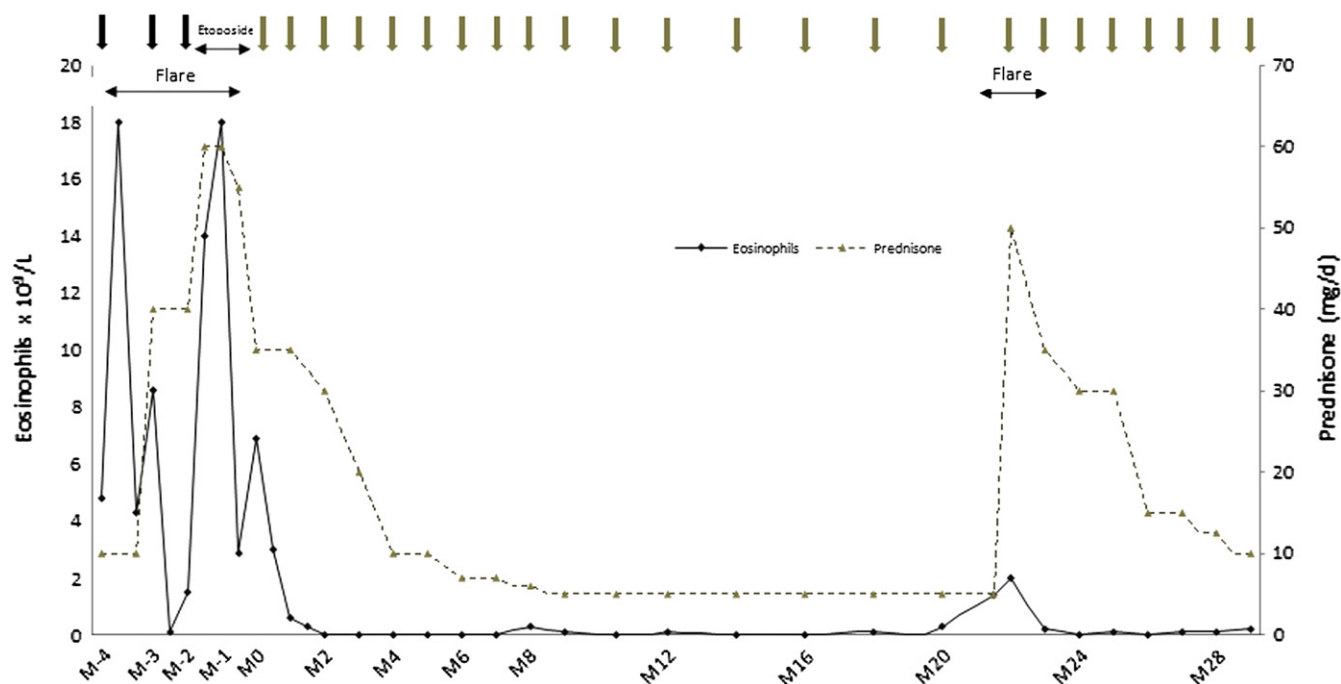


FIG 1. Eosinophil count and prednisone dosage before and during mepolizumab treatment. *Black arrows* represent monthly pulses of cyclophosphamide, 1 g intravenous. *Gray arrows* represent infusion of mepolizumab, 750 mg intravenous. *M*, Month.

flow = 220 L/min), and eosinophilia relapsed (Fig 1). Chest computed tomography revealed bilateral, patchy, nonsegmental ground glass attenuation with peripheral upper lung distribution, interlobular septal thickening, areas of consolidation, and bronchial wall thickening in the lower lobes. Etoposide was introduced (100 mg/d for 7 days every 3 weeks), and transient lowering of eosinophil counts was observed after the first course (Fig 1), but thoracic imaging remained unchanged (Fig 2, A), and complete alopecia occurred. Because the disease was not controlled, therapy with mepolizumab (750 mg/mo intravenous) was started in June 2007. Authorization for temporary use was obtained from the French sanitary security committee, and informed consent was obtained from the patient. Asthma significantly improved after the first infusion and disappeared within 6 months (peak flow returned to baseline value, and inhaled treatments were stopped). The eosinophil count decreased, reaching normal values after 1 month (Fig 1). Chest computed tomography examinations performed before the second infusion showed complete regression of parenchymal findings (Fig 2, B), persisting after 6 months (Fig 2, C). An attempt to increase the intervals progressively between mepolizumab infusions to 2 months resulted in a relapse at month 20, with reappearance of asthma, interstitial lung infiltrates, and increases of eosinophils to $2 \times 10^9/L$. All parameters normalized in 1 month with transient increase of prednisone. Eight months after this relapse, this previously refractory disease is still controlled with monthly mepolizumab infusions, and small doses of steroids, whereas other immunosuppressive agents could be stopped for more than 2 years. No allergic reaction arose. Two episodes of acute bronchitis and 1 of pneumonia occurred during follow-up, requiring ambulatory care. Such adverse events have not been reported in clinical trials using mepolizumab in asthma or hypereosinophilic syndrome and may be linked to previous long-term immunosuppressive therapy. Of

note, we did not observe qualitative or quantitative modification of T-cell and B-cell subsets or γ -globulin levels (data not shown).

Recent studies have suggested that ANCA-negative status in CSS is associated with a nonvasculitic pattern, including more frequent cardiac or pulmonary involvement (excluding pulmonary hemorrhage) and a low frequency of glomerulonephritis, purpura, and mononeuritis multiplex.¹ The ANCA-negative CSS profile may be difficult to distinguish from hypereosinophilic syndrome, in which mepolizumab has a steroid sparing effect.² The effectiveness of mepolizumab in our case is strengthened by the demonstration that the disease activity flares after spacing infusions, and that retreatment with monthly doses further controls the disease.

In addition to the normalization of blood eosinophil counts, the complete normalization of chest computed tomography scans and the clinical control of asthma suggest clearance of tissue eosinophils (pulmonary and bronchial) in our patient, which is a major objective when treating eosinophilic disorders. The reduction of ECP levels observed during mepolizumab treatment is consistent with reduced activation and degranulation of eosinophils. The regression of asthma in our patient is in apparent contradiction to the absence of clinical benefit with mepolizumab in patients with conventional asthma.³ However, in a subgroup of patients with refractory eosinophilic asthma (defined by a sputum eosinophil percentage above 3%), probably closer to asthma observed in CSS, 2 recent studies have shown that mepolizumab improves control of asthma.^{4,5} These data suggest a different, and possibly more pivotal, role for eosinophils in eosinophilic asthma and CSS-related asthma than conventional allergic asthma.

The high serum IL-5 levels observed at baseline in our patient have been reported by others in patients with CSS.⁶⁻⁸ However, anti-IL-5 therapy has been shown effective in hypereosinophilic syndrome regardless of the ability to demonstrate IL-5

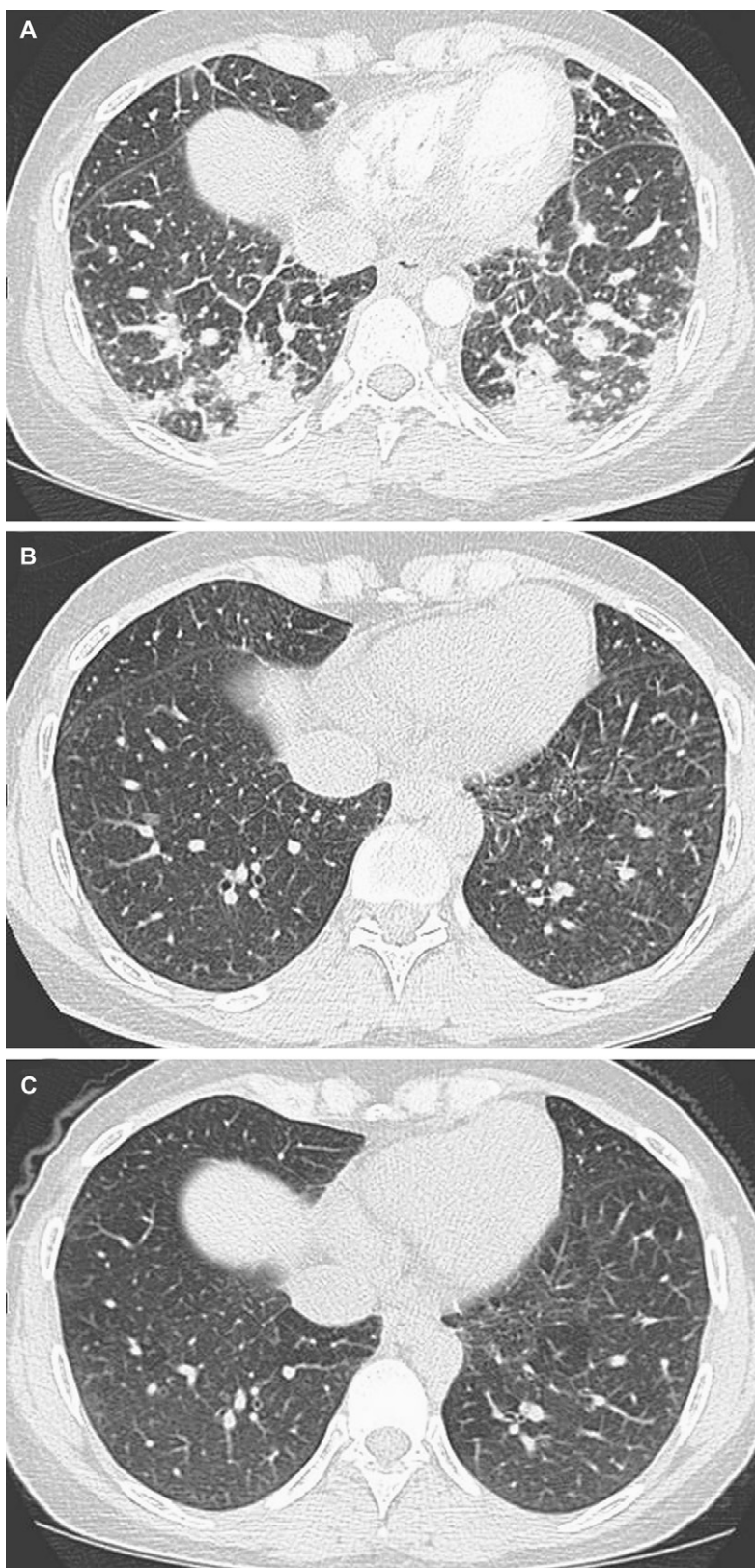


FIG 2. Computed tomography of the chest before mepolizumab (**A**) and 1 month (**B**) and 6 months (**C**) after mepolizumab initiation.

overproduction or not. The further increase in serum IL-5 observed during treatment with mepolizumab has been described in other studies.^{2,9}

In summary, our observation suggests that mepolizumab may represent a novel suitable therapeutic option in refractory CSS. The marked, sustained clinical and biological improvement observed by using mepolizumab also highlights the pivotal role of IL-5 and eosinophils in ANCA-negative CSS, probably underestimated to date. Although further studies are needed to confirm these preliminary data, a new therapeutic approach in CSS based on antieosinophil drugs may be promising.

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REFERENCES

1. Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum* 2005;52:2926-35.
2. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008;358:1215-28.
3. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356:2144-8.
4. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
5. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
6. Kojima K, Omoto E, Katayama Y, Uno M, Takada I, Kimura G, et al. Autoimmune hemolytic anemia in allergic granulomatous angitis (Churg-Strauss syndrome). *Int J Hematol* 1996;63:149-54.
7. Shiota Y, Matsumoto H, Kanehisa Y, Tanaka M, Kanazawa K, Hiyama J, et al. Serum interleukin-5 levels in a case with allergic granulomatous angitis. *Intern Med* 1997;36:709-11.
8. Termeer CC, Simon JC, Schopf E. Low-dose interferon alfa-2b for the treatment of Churg-Strauss syndrome with prominent skin involvement. *Arch Dermatol* 2001;137:136-8.
9. Stein ML, Villanueva JM, Buckmeier BK, Yamada Y, Filipovich AH, Assa'ad AH, et al. Anti-IL-5 (mepolizumab) therapy reduces eosinophil activation ex vivo and increases IL-5 and IL-5 receptor levels. *J Allergy Clin Immunol* 2008;121:1473-83.e4.

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Persistent rotavirus vaccine shedding in a new case of severe combined immunodeficiency: A reason to screen

To the Editor:

Rotavirus infections in the United States have decreased as a result of vaccination efforts. Before 2006, when the vaccine was implemented, the burden of disease was high, with approximately 27,000 to 70,000 children under 5 years of age hospitalized with

rotavirus infection and about 20 to 60 reported deaths annually according to the Centers for Disease Control and Prevention and other studies.¹⁻⁵ Since the introduction of vaccination, rotavirus rates in the United States have diminished by more than 50%, translating to the prevention of 48,000 hospitalizations and 30 deaths.^{2,4,5} Studies have also shown a delay in the seasonal onset of the disease by 2 to 4 months.^{4,7} Cost savings to the medical community with the vaccines are estimated to be as much as \$198,000 per life-year.⁸ The question arises, however, as to the unforeseen costs on a population of patients with undiagnosed immune deficiency. In March 2009 there were 2 reported cases by Patel et al⁹ of rotavirus infection from RotaTeq (Merck and Co, Inc, Whitehouse Station, NJ) vaccine strains in unknown cases of SCID (severe combined immune deficiency) with adenosine deaminase deficiency and IL-2 receptor- γ deficiency. Werther et al¹⁰ also recently described a 9-month-old girl with a new diagnosis of unspecified SCID who shed the RotaTeq virus strain for 7.5 months and finally cleared it posttransplant. All 3 of these patients presented with gastrointestinal symptoms and failure to thrive. Vaccine strains were identified by RT-PCR.

The patient reported here is a 5-month-old boy born to non-consanguineous parents who presented with lethargy, dehydration, and failure to thrive. He had developed chronic diarrhea beginning at 2 months of age and had poor weight gain over the month before admission. He had been vaccinated with RotaTeq at 2 and 4 months. Before his admission, a stool sample had grown *Salmonella*. His blood cultures on admission grew *Salmonella* that was promptly treated with antibiotics. Further testing of his stool revealed *Rotavirus* antigen as well as persistent *Salmonella*. A diagnosis of SCID was suspected and then confirmed (T^B NK⁻, IL-2RG mutation). He quickly decompensated after 48 hours of admission with onset of respiratory distress and was diagnosed by bronchoscopy to have *Pneumocystis jirovecii*. A stool sample was assessed by RT-PCR for the genes *VP6* and *NSP1*. They matched the RotaTeq vaccine strain exactly. One month later, he continued to demonstrate rotavirus antigen in his stool. He is currently awaiting stem cell transplant by an unrelated matched donor. RotaTeq virus shedding is expected from 1 to 15 days in 9% after first dose and in 0.3% after the third dose in healthy children.¹¹

This case and the previously reported cases bring into question current vaccination practices. The updated American Academy of Pediatrics guidelines pose vaccination of immunocompromised children as a precaution. They clearly state that immunodeficient children might be at risk for severe or prolonged gastroenteritis.⁸ However, the timing of the vaccination does not allow patients with congenital immune deficiency sufficient time to declare themselves. There is no question about the substantial benefit from the vaccine in reducing morbidity as well as health care costs in the United States for the general population. Risks of the vaccine to immunocompromised hosts do not negate its widespread use, but rather reinforce the need for neonatal screening measures of SCID in particular.

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