

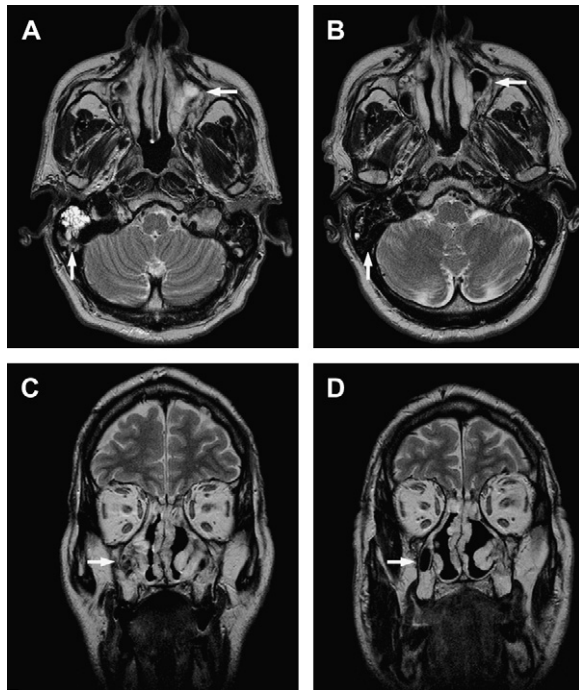


FIG 1. MRI scans demonstrate the improvement of mastoiditis, sinus ventilation, and mucosal edema after anti-IgE treatment (**B, D**) in contrast with pretreatment MRI (**A, C**). The reduction of mucosa swelling and the increase of nasal patency enables the patient to undergo a 20-minute closed-mouth scan without any difficulties (**D**), in contrast with the open-mouth scan necessary for the pretreatment condition (**C**).

a chronic but asymptomatic mastoiditis was diagnosed by magnetic resonance imaging (MRI; Fig 1).

Hence, in 2006 we initiated a therapy with 225 mg omalizumab biweekly (calculated for a body weight of 83 kg and total serum IgE level of 216 kU/L). Asthma symptoms clearly ameliorated within 2 months, and the patient reported a significant reduction of his sinus complaint. Chronic forehead and paranasal pressure as well as retranasal mucus were eliminated, and his sense of smell was restored. Four months after therapy initiation, a resolution of nasal mucosa swelling and a reduction of polypoid swelling and inflammation of the entire paranasal sinus were documented by MRI. The chronic mastoiditis had been completely eliminated (Fig 1). Thus MRI scan results coincide with the patient's report. Although computed tomography scans are the typical approach for the diagnosis of chronic rhinosinusitis, MRI scans were conducted in this case because of the lower radiation exposure with repeated examination.

Omalizumab is a humanized anti-IgE antibody approved for treatment of moderate to severe persistent asthma when a positive skin test or *in vitro* reactivity to a perennial aeroallergen is documented, and if symptoms are inadequately controlled by inhaled corticosteroids and inhaled long-acting β_2 -agonists.⁵ The efficacy of omalizumab has been clearly demonstrated for this indication by several clinical studies.⁶ Furthermore, the benefit of omalizumab for patients with allergic asthma and associated allergic rhinitis has been demonstrated in the Study of Omalizumab in Comorbid Asthma and Rhinitis (SOLAR).⁷

Our report suggests that omalizumab can be effective in the treatment of chronic rhinosinusitis. We observed not only a resolution of nasal mucosa swelling (in accordance with the

SOLAR study) but also a reduction of polypoid swelling and inflammation of the entire paranasal sinuses, and a complete healing of chronic mastoiditis. The anti-IgE therapy reduces the allergic inflammation, and our case report gives further evidence for an IgE-mediated mechanism (IgE antibodies to bacterial superantigens and aeroallergens) in the pathophysiology of chronic rhinosinusitis at least in some patients. To broaden the therapeutic applications of omalizumab, further studies must be conducted.

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The effect of etanercept on the human cutaneous allergic response

To the Editor:

Etanercept (Enbrel; Immunex Corp, Thousand Oaks, Calif) is a TNF receptor 2-Fc fusion protein approved for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and psoriasis. It antagonizes the actions of both TNF- α and TNF- β , but most of its clinical efficacy is the consequence of TNF- α antagonism. TNF- α is a potent multifunctional cytokine produced by a wide variety of cell types and is important for host defense and inflammatory cell influx and activation.¹ Recent studies have demonstrated that TNF- α levels are elevated in the lungs of patients with severe asthma, and neutralizing its activity may be an effective treatment.²⁻⁴ To date, however, no human studies have been conducted to explore the effect of TNF- α inhibition on allergic inflammation in the skin. We conducted this open trial to determine whether systemic administration of etanercept at doses effective for psoriasis could affect allergic responses in the skin.

This trial was approved by the institutional review board at Johns Hopkins University, and informed consent was obtained from each participant. Subjects between the ages of 18 and 65 years were enrolled if they had perennial allergic rhinitis and demonstrated a wheal size with mean diameter ≥ 12 mm 15 minutes after intradermal injection with one of the dust mite allergens (*Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*; Greer Laboratories, Lenoir, NC). Exclusion criteria included any of the following: history of multiple sclerosis, optic neuritis, myelitis, lidocaine allergy, keloids, active tuberculosis, or a positive purified protein derivative test result without receiving appropriate medical therapy. Subjects were off antihistamines, antileukotrienes, and topical or systemic corticosteroids for at least 7 days before and throughout the study.

This was an open-label trial using intradermal skin test titration with increasing concentrations of *D pteronyssinus* or *D farinae*. The dose that achieved a wheal size with a mean diameter ≥ 12 mm was defined as dose X. The following week, dose X was injected into 2 locations on the volar forearm, and a 5-mm skin biopsy was performed 2 and 16 hours later. Etanercept 50 mg was administered subcutaneously immediately after the final skin biopsy, with 2 more doses given at 72-hour intervals. All doses were administered by study personnel. Twenty-four hours after the third and final dose of etanercept, 2 more intradermal injections of dose X were performed on the contralateral volar forearm, and skin biopsies were performed 2 and 16 hours later. Subjects returned in 14 days for a final visit to assess adverse events from the skin biopsies or etanercept treatment. Serum was obtained 16 hours after allergen challenge both before (eg, baseline measurement) and after etanercept treatment to measure drug levels.

The acute-phase response (APR) at 15 minutes and the late-phase response (LPR) at 16 hours were traced onto Scanpor tape (3M, St Paul, Minn). This tracing was scanned, and the area was measured in pixels (Image J software; National Institutes of Health, Baltimore, Md). A visual analog scale (0-10) was used to quantify pruritus during the APR and LPR using the phrase, "How much does your skin itch?" Etanercept levels in serum were measured by using an ELISA assay (Amgen, Thousand Oaks, Calif). The sensitivity of the assay was 0.62 ng/mL.

Formalin-fixed and paraffin-embedded skin sections were stained to enumerate eosinophils (EG2; Kabi Pharmacia, Rockville, Md), neutrophils (neutrophil elastase; Zymed, Carlsbad, Calif), macrophages (CD68; Dako, Carpinteria, Calif), T lymphocytes (CD3; Dako), cutaneous lymphocyte antigen (HECA452;

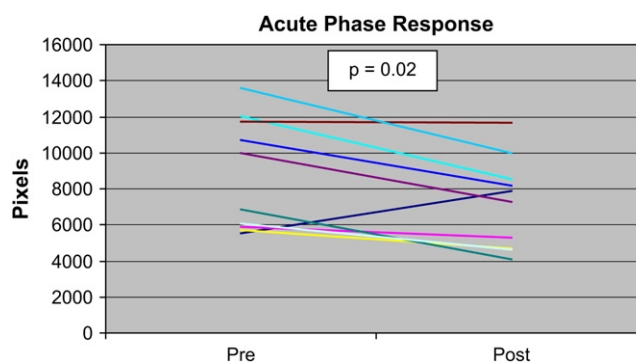


FIG 1. Effect of etanercept administration (Post) on the area of the APR measured at 15 minutes ($\Delta P = .02$).

BD Pharmingen, San Jose, Calif), and the expression of the endothelial adhesion molecules, vascular cell adhesion molecule 1 (VCAM-1), and E-selectin (R & D Systems, Inc, Minneapolis, Minn) as described previously.⁵ All comparisons were made using the Wilcoxon signed-rank test.

Ten subjects were enrolled and completed the trial. The mean age was 38 ± 3 years, with 6 male and 4 female subjects. Etanercept was well tolerated. Serum etanercept levels increased in all subjects from undetectable to 5849 ± 746 ng/mL (range, 2700-9800 ng/mL; $P < .01$).

Unexpectedly, a significant reduction in the size of the APR was observed after administration of etanercept ($P = .02$; Fig 1). The mean reduction of wheal size diameter was $16\% \pm 7.3\%$. No difference, however, was noted for the size of the LPR at 16 hours ($P = .6$). Subject-reported itch scores did not change after etanercept at either the APR or LPR time points (data not shown). A statistically significant increase in EG2⁺ ($P = .04$) and CD3⁺ cells ($P = .001$) was observed between the 2-hour and 16-hour biopsies without etanercept treatment, demonstrating that a robust cellular LPR was elicited with the allergen doses used. However, 3 doses of etanercept had no effect on the numbers of eosinophils, neutrophils, lymphocytes, or CD68⁺ macrophages observed in skin biopsies taken 2 or 16 hours after allergen injection (Table I). Similarly, there were no significant changes in the percentage of blood vessels that stained positively for VCAM-1 or E-selectin after the administration of etanercept.

TNF- α is thought to be important in allergic inflammation because it is released by mast cells and is a potent inducer of

TABLE I. Measurement of cellular infiltrate and endothelial adhesion molecules in EPR and LPR skin biopsies before and after etanercept treatment

	2 h				16 h			
	Pre Rx (SD)	Post Rx (SD)	Mean change (SD)	P value	Pre Rx (SD)	Post Rx (SD)	Mean change (SD)	P value
Cells/mm ²								
EG2 ⁺	77 (53)	116 (84)	+38 (69)	.14	167 (144)	151 (80)	-16 (147)	.68
Neutrophil elastase ⁺	471 (129)	472 (167)	+1 (124)	.51	436 (165)	411 (182)	-25 (187)	.37
CD3 ⁺	17 (20)	20 (23)	+3 (4)	.10	71 (37)	71 (42)	+0.1 (42)	.61
Cutaneous lymphocyte antigen ⁺	8 (11)	7 (4)	-1 (8)	.99	14 (12)	10 (7)	-4 (7)	.42
CD68 ⁺	161 (136)	156 (133)	-5 (141)	.96	188 (96)	254 (171)	+66 (118)	.20
Percent of positive vessels								
E-selectin*	56 (21)	59 (17)	+1 (16)	.96	48 (21)	52 (27)	4 (26)	.59
VCAM-1*	1.8 (4)	1.6 (4)	-0.2 (2)	.99	2.3 (4)	2.3 (3)	0 (4)	.75

*Listed as a percentage of endothelial cells staining positive for adhesion molecule.

endothelial adhesion molecule expression and chemokine production.^{6,7,11,12} Several publications have suggested that TNF antagonism is an effective therapy in specific asthma subsets.¹⁻³ Using a model of cutaneous allergic inflammation, we observed a modest reduction in the size of the APR with no effect on the size, symptoms, or cellular features of the LPR. The lack of an LPR effect is not likely a result of inadequate cutaneous absorption of etanercept, because expected blood levels were achieved in all subjects, and the dose used in this study is effective in psoriasis. It therefore seems probable that the lack of an effect on the LPR reflects the biology of this model. Our results coupled with 2 case reports demonstrating little to no effect with the TNF antagonists infliximab or etanercept in subjects with atopic dermatitis (AD)^{8,9} strongly suggest that AD, and the cutaneous LPR as a model of AD, are not TNF-mediated.¹³⁻¹⁵

Etanercept significantly reduced the size of the APR, which is consistent with the observation that sputum histamine was reduced in a recent study of etanercept (25 mg twice weekly) treatment in subjects with refractory asthma.³ It is therefore possible that etanercept inhibits the priming action of TNF- α on IgE-mediated mast cell histamine release or that it inhibits direct TNF- α effects such as the release of neurotransmitters from nerve endings in the skin, both of which are worthy of further study. Last, our finding suggests that etanercept may be an effective treatment for urticaria, as has been shown in a recent case report.¹⁰

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IL-1 blockade in Schnitzler syndrome: *Ex vivo* findings correlate with clinical remission

To the Editor:

Schnitzler syndrome is a disease characterized by chronic urticaria with intermittent fever, arthralgia, and a monoclonal gammopathy. Recently, the use of IL-1 inhibitors has been advocated on the basis of clinical observations.¹ In this report, we examine the *ex vivo* production of cytokines and effect of inhibition of IL-1 in Schnitzler syndrome.

A 50-year-old white woman with an 8-year history of increasingly severe urticaria presented for evaluation. She initially noticed intermittent, scattered, nonpruritic "hive"-like rashes presenting for a few hours at a time. The rash gradually progressed to chronic persistent urticaria with significant pruritus, affecting her entire body with the exception of her face. She had a 3-year history of intermittent fever up to 39°C, with associated fatigue, myalgia, and arthralgia affecting her lower limbs. She denied perioral edema or dyspnea. Previous trials of numerous medications, including antihistamines and montelukast, were unsuccessful; high doses of steroids resulted in temporary improvement. Past history included hypothyroidism for which she was on an adequate dose of levothyroxine.

On examination, she had indurated erythematous papules and plaques, ranging in size from 0.5 to 4 cm in diameter, with the most prominent involvement on the central body (Fig 1, A). No pigmentary disturbance, bruising, or epithelial change was noted. Laboratory tests revealed anemia (hemoglobin 101 g/L), thrombocytosis (platelets $749 \times 10^9/L$), and white cell count of $6.9 \times 10^9/L$. Complement levels, including functional assays, were normal. Biochemistry was normal except for elevated alkaline phosphatase at 146 U/L and IgM gammopathy with a total IgM of 9.22 g/L on serum protein electrophoresis, with no paraprotein peak on urine protein electrophoresis. Bone marrow biopsy demonstrated no increase in lymphocytes, blast cells, or plasma cells. Flow cytometry showed no clonal population. Bone scintigraphy showed increased uptake in both tibiae. Biopsy of affected skin demonstrated a neutrophilic dermatosis with no evidence of vascular damage.

A diagnosis of Schnitzler syndrome was reached. This syndrome bears similarities to Muckle-Wells syndrome (MWS), an inherited disease in which symptoms usually begin in childhood and mutations in the *CIAS1* gene are found. Sequencing of the entire gene in this patient revealed no mutations.