

Desensitization was approached using a standard protocol beginning at 1/10,000 (0.02 mg) or 1/10 of the bioassay skin test concentration (1/1,000) of the expected dose (200 mg) and doubling every 15 minutes until approximately 200 mg was administered. After oral desensitization to an approximately 197-mg total dose (Table 1), 200 mg/d was then administered for 14 days, beginning the following day. In July 2004, she developed transient hives 2 hours after desensitization, which resolved with antihistamine within the week. In April 2007, with her fifth desensitization, she developed disseminated, flat, 2- to 7-cm circular lesions in the right frontal and right precordial areas beginning 4 hours after desensitization. These lesions progressed to a macular rash that was pruritic beginning 4 hours after desensitization and generalizing by 48 hours. There was a single blistered lesion in her right frontal and axillary area. She was treated with prednisone, beginning at 60 mg and tapered 10 mg/d, and diphenhydramine, 25 mg every 4 hours, with resolution of her rash within the week. She completed 2 weeks of fluconazole therapy as prescribed. In September 2007, she was taking prednisone, 10 mg/d, for an asthma exacerbation at desensitization but discontinued prednisone therapy. A transient exanthem developed that was diffuse and maculopapular, involving the upper torso and extremities only, with an isolated blistered vesicle beginning 4 hours after desensitization. The vesicle resolved within 3 days after completing 48 hours of prednisone therapy, 60 mg/d.

CHRIS RANDOLPH, MD

CYNTHIA KAPLAN, RN

BARBARA FRASER, LPN

Center for Allergy, Asthma, and Immunology
Waterbury, Connecticut

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REMISSION OF SCHNITZLER SYNDROME AFTER TREATMENT WITH ANAKINRA

Schnitzler syndrome is a rare and underrecognized disorder characterized by chronic urticarial rash, IgM (or rarely IgG) monoclonal gammopathy, and at least 2 of the following: recurrent fevers, arthralgia, bone pain, lymphadenopathy, hepatosplenomegaly, elevated inflammatory markers, leukocytosis, and abnormal bone morphology.¹ Because the clinical signs associated with Schnitzler syndrome are varied, patients are often evaluated by multiple specialists before a diagnosis is made. Correct diagnosis of Schnitzler syndrome is essential because approximately 15% of patients will develop lymphoproliferative disease, and, therefore, long-term follow-up is important.¹

No approach has been consistently effective in treating the urticarial rash associated with Schnitzler syndrome. H₁/H₂ blockers, inhibitors of neutrophil migration (dapson, colchicine), plasmapheresis, and intravenous immunoglobulin have not been effective.¹ A few case reports^{1–3} have suggested improvement with high-dose corticosteroids, thalidomide, and quinolones, but these treatments are not universally effective, and widespread clinical use is limited by their associated adverse effects.

We describe a 72-year-old man who was evaluated for a 2-year history of diffuse urticaria. The rash consisted of moderately pruritic, rose-colored, mildly edematous oval lesions that occurred daily and typically resolved without residual skin changes after 24 to 48 hours (Fig 1). Skin biopsy revealed a perivascular infiltrate of predominantly mononuclear cells. The patient never experienced angioedema. During the ensuing year, he developed a nonproductive cough, daily low-grade fevers, intermittent night sweats, bone pain, a 10-lb weight loss, and palpable inguinal and axillary lymph nodes. He also complained of breast tenderness and swelling. Laboratory studies showed a moderately elevated erythrocyte sedimentation rate of 32 mm/h and a C-reactive protein level of 8.3 mg/L. Blood cell count revealed leukocytosis (22,200/mm³ with 89% neutrophils), anemia (hemoglobin level, 10.4 g/dL), and thrombocytosis (522 k/mm³). Results of complement and thyroid studies were normal. Luteinizing hormone, follicle-stimulating hormone, and prolactin levels were normal. Serum immunoglobulins showed mildly elevated IgG (1,760 mg/dL) and IgM (304 mg/dL) levels and a normal IgA level (127 mg/dL). Serum protein electrophoresis demonstrated a monoclonal IgM protein with κ light chains on immunofixation. No Bence-Jones proteinuria was evident. A chest computed tomograph demonstrated bilateral axillary lymphadenopathy and gynecomastia, and an abdominal/pelvic computed tomograph showed bilateral enlarged inguinal nodes. Results of purified protein derivative of tuberculin testing were negative. An inguinal lymph node biopsy revealed reactive follicular and interfollicular lymphoid hyperplasia, and a bone marrow biopsy specimen demonstrated

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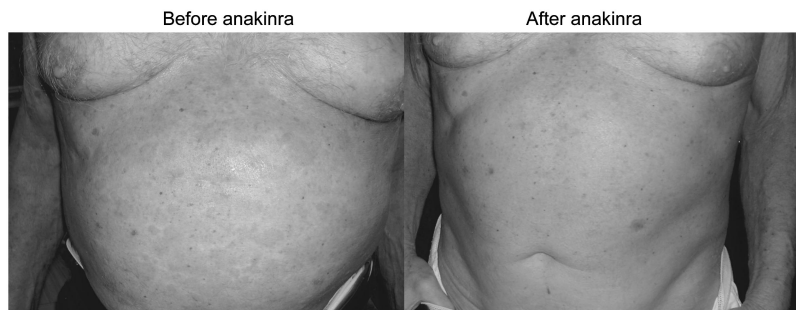


Figure 1. Diffuse urticaria on the stomach (left), with near complete resolution after starting anakinra therapy (right).

mildly hypercellular marrow with slight granulocytic hyperplasia (51% neutrophils) but no evidence of lymphoproliferative disease.

Attempted therapies included diphenhydramine, doxepin, cetirizine, fexofenadine, montelukast, and topical high-potency corticosteroid preparations, and all were ineffective. The patient was subsequently treated with a 1-month course of prednisone (20 mg/d) and experienced improvement in cough and fevers and a slight decrease in urticarial lesions, but all symptoms returned to pretreatment severity once the dose was weaned to 5 mg/d. He was subsequently given the interleukin 1 (IL-1) antagonist anakinra (Kineret; Amgen Inc, Thousand Oaks, California), 100 mg/d subcutaneously, and experienced a dramatic improvement in urticaria, bone pain, cough, and fever within a few days and a gradual improvement in lymphadenopathy during the subsequent 2 to 3 weeks (Fig 1). In addition, hemoglobin, white blood cell, and platelet counts normalized during this period. Approximately 1 month after starting anakinra therapy, he discontinued treatment owing to difficulties with insurance coverage; within 24 hours he had complete recrudescence of cough, urticaria, bone pain, and fevers, as well as laboratory studies. All these symptoms rapidly resolved once anakinra therapy was reinitiated. The patient currently remains almost entirely free of urticaria, fevers, bone pain, and cough. He continues to have very mild pruritus and gynecomastia, although both are remarkably improved since starting anakinra therapy. He has tolerated the treatment with occasional mild injection site reactions but no infections or other untoward effects. A complete blood cell with differential count is monitored monthly while he continues therapy.

Anakinra is a recombinant form of human IL-1Ra, a natural protein that neutralizes the biological activity of IL-1 by competitively inhibiting IL-1 binding to IL-1R1. Anakinra has proven therapeutic benefit in patients with rheumatoid arthritis and other inflammatory conditions.⁴ The present study, and a few others,^{5,6} suggests that anakinra may be an effective, well-tolerated treatment for Schnitzler syndrome as well. A specific role for IL-1 in the pathogenesis of Schnitzler syndrome is unclear. In 1 study,⁷ serum samples from 6 of 9 patients with Schnitzler syndrome were found to contain

anti-IL-1 α IgG autoantibodies. These antibodies are thought to prolong the half-life of IL-1 and perhaps enhance its effects. However, subsequent studies did not replicate these findings, and the exact pathogenesis remains unknown.⁸

Schnitzler syndrome should be considered in all patients with recalcitrant chronic urticaria in the setting of monoclonal gammopathy. Anakinra is a promising therapeutic option for these patients. Further information regarding Schnitzler syndrome can be found at <http://www.schnitzlersyndrome.com>.

PAMELA A. FRISCHMEYER-GUERRERIO, MD, PhD
Division of Allergy and Immunology
Department of Pediatrics
The Johns Hopkins University School of Medicine
Baltimore, Maryland

RADHIKA RACHAMALLA, MD
Cancer Center of Poughkeepsie
Poughkeepsie, New York

SARBJIT S. SAINI, MD
Division of Allergy and Clinical Immunology
Department of Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland

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EXTRAPOLATION OF ALLERGEN PC₁₅

Although allergen inhalation tests are usually performed to look at the late asthmatic response, studies addressing the early asthmatic response (EAR) have also been performed.^{1–4} In such studies, the EAR is expressed as the provocation concentration producing a 15% or 20% decrease in forced expiratory volume in 1 second (FEV₁) (PC₁₅ or PC₂₀, respectively). The PC₁₅ is calculated by interpolation of the log (doubling) dose vs response curve by an algebraic equation analogous to that used to calculate the methacholine PC₂₀.⁵ The dose-response curve to allergen is frequently steep. To prevent marked decreases in FEV₁ after allergen, it would be valuable to be able to accurately extrapolate the allergen PC₁₅ from an FEV₁ decrease of less than 15%, thereby avoiding the next doubling dose with its predictable larger FEV₁ decrease, especially in study protocols in which administration of rescue β -agonist is to be avoided when safety permits. The methacholine PC₂₀ can be accurately extrapolated from a 15% to 19% FEV₁ decrease.⁶ A retrospective analysis of data from previously published allergen-induced EAR studies was performed to evaluate the accuracy of extrapolation of allergen PC₁₅ from an 11% to 15% decrease in FEV₁.

The following analysis was performed in 25 subjects (mean [SEM] age, 26.3 [1.3] years), 15 of whom were female, participating in 4 published EAR studies.^{1–4} The first allergen challenge in each individual meeting the following criteria was selected for analysis. The allergen challenge produced an 11% to 14% FEV₁ decrease (R1) at the second last concentration (C1) and a greater than 15% FEV₁ decrease (R2) at the final (doubling) concentration (C2). The PC₁₅ was interpolated by the following logarithmic formula⁵:

$$PC_{15} = \text{Antilog} [\log C1 + (\log C2 - \log C1) \times (15 - R1)/(R2 - R1)]$$

The PC₁₅ was also extrapolated from the second last concentration (C1) as follows⁶: PC₁₅ = C1 $\times$ (15/R1).

Little difference was seen in individual data or in mean data (geometric mean interpolated PC₁₅ of 209 allergen units per milliliter vs geometric mean extrapolated PC₁₅ of 218 allergen units per milliliter) (Figure 1). This small difference was statistically significant ($P = .03$ by paired t test) because of a tendency (18 of 25 subjects) for the extrapolated PC₁₅ to slightly overestimate the PC₁₅ because of a steep dose-response slope.

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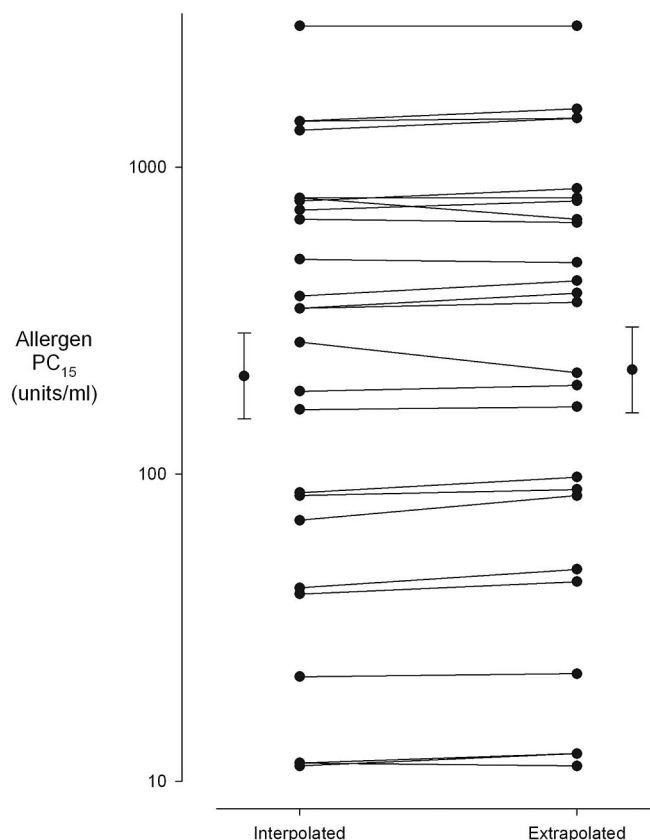


Figure 1. Interpolated allergen provocation concentration producing a 15% decrease in forced expiratory volume in 1 second (PC₁₅) and extrapolated allergen PC₁₅. Error bars indicate geometric mean PC₁₅ and geometric SE.

These data suggest that the allergen PC₁₅ (or PC₂₀) can be acceptably extrapolated from a slightly less than 15% (or analogously slightly less than 20%) FEV₁ decrease. This has several advantages. First, it will prevent at least occasional large and uncomfortable FEV₁ decreases in studies that are exclusively performed in research volunteers; these research protocols often require repeated allergen challenges. Second, it will minimize the likelihood of the occurrence of significant late asthmatic responses that will be more likely to occur or be larger when the allergen dose is doubled. Third, it may obviate the need for administration of rescue β -agonist.

DONALD W. COCKCROFT, MD, FRPC(C)
BETH E. DAVIS, BSc
Division of Respiriology, Critical Care, and Sleep
Medicine
Department of Medicine
Royal University Hospital
University of Saskatchewan
Saskatoon, Saskatchewan, Canada