

similar improvement in ocular symptoms compared with an oral antihistamine (loratadine) in patients with SAR (Table 1).⁵ Overall, the reduction in ocular symptom scores was less than 46% but similar to the effects on ocular symptoms by other intranasal steroids.

To date, prospective comparative data on the ocular safety of triamcinolone acetonide aqueous nasal spray are not available. Although insufficient evidence exists to support an association between INS and the development of cataracts and/or glaucoma at licensed doses, periodic monitoring is warranted in patients with a high predisposition to either condition.

These data may further the argument for a class effect of INS in the treatment of the ocular symptoms associated with AR because triamcinolone acetonide and other INS in these studies demonstrate a potential positive impact on ocular allergy symptoms.^{6,7} It would appear that to maximize the impact of INS use of the drugs should be started before the patient's allergy season. Given the established efficacy of INS in reducing nasal symptoms, such a treatment approach in patients with AR may reduce the need for multiple medications, potentially resulting in increased adherence and improved patient outcomes.

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CHRONIC URTICARIA CAUSED BY FOLIC ACID

A 72-year-old woman presented with an 8-month history of daily urticaria and occasional facial angioedema. She received antihista-

mines but was free of hives only for a few hours each day. Four years ago, she was diagnosed as having autoimmune hemolytic anemia/thrombocytopenia (Evans syndrome) and was treated with prednisone. Because of the adverse effects of the treatment, her therapy was changed to azathioprine, 50 mg/d, 3 years ago, and folic acid, 400 μ g/d, 2 years ago. She had no history of intake of non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, or other medications and no previous drug reactions.

No wheals, dermographism, organomegaly, or lymphadenopathy were present on physical examination. Laboratory data showed a hemoglobin level of 13.7 g/dL (reference range, 12–16 g/dL); hematocrit, 39.9% (reference range, 37%–47%); platelets, $203 \times 10^3/\mu$ L (reference range, 150–450 $\times 10^3/\mu$ L); and leukocytes, $3.5 \times 10^3/\mu$ L (reference range, 6–19 $\times 10^3/\mu$ L). Polyclonal hypergammaglobulinemia was detected. The levels of analytes were as follows: serum globulin, 4.80 g/dL (reference range, 1.5–3.0 g/dL); γ -globulins, 28.2% (reference range, 10%–19%); IgG, 3,729 mg/dL (reference range, 1,000–2,100 mg/dL); IgA, 525 mg/dL (reference range, 100–500 mg/dL); and IgM, 273 mg/dL (reference range, 44–290 mg/dL). The results of antibody tests directed against hepatitis B and C, nuclear, thyroglobulin, thyroid peroxidase, DNA, mitochondrial, and lupus anticoagulant antigens were negative. We suspected that folic acid was the possible cause of the urticaria, and its use was discontinued. Azathioprine therapy was maintained. A few days later, the urticaria disappeared.

One month after discontinuation of folic acid use, prick and intradermal tests were performed with folic acid, 1 and 5 mg/mL, while the patient was using azathioprine and after the patient stopped using azathioprine for a week. The results were negative. Histamine phosphate, 10 mg/mL, used as a positive control produced a 5-mm papule with a 7-mm flare in the prick test and a 12-mm papule with a 15-mm flare in the intradermal test. The results of single-blind oral challenge tests with increasing doses of folic acid, 1 mg/mL, administered at 30-minute intervals (0.25, 0.50, and 1 mL) were positive. Ten minutes after the 1-mL dose, the patient developed red pruriginous wheals. Generalized urticaria, facial and lingual edema, and bilateral conjunctival congestion were observed 2 hours later. The patient's arterial blood pressure and pulse remained stable. The results of the oral challenges were negative, with placebo and folic acid excipients. Folic acid specific IgE testing was performed using the enzyme-linked immunosorbent assay method,¹ with some modifications. The result was negative. Histamine release tests were not performed.

Three weeks after the folic acid challenge, a single-blind parenteral challenge test with folic acid, 50 mg/5 mL, was performed. One hour after the 5-mL intramuscular dose, the patient developed a red pruriginous macule (10 $\times$ 8 cm) over her torso. There were no reactions at the site of injection (left arm). We believed that if we increased the folic acid dose, the patient would have had an unnecessary generalized reaction. The patient was advised to discontinue folic acid treatment. Six months later, she remained free of urticaria.

Hypersensitivity reactions to folic acid are extremely unusual; to our knowledge, only 7 cases have been reported in the literature.^{2–8} In this study, the relationship between chronic urticaria and folic acid has been strongly suggested through the discontinued use of the drug and the resulting permanent control of the urticarial symptoms. This was additionally confirmed through the positive oral challenge test result. The negative skin test and enzyme-linked immunosorbent assay results suggest a non-IgE-mediated condition evolving in our patient. Folic acid also produced a positive reaction after the parenteral challenge test. Clinical and immunological cross-reactivity was previously described by Dykewicz et al.⁴ Contrary to the

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report of Sanders and Fritz,³ our patient has demonstrated a good tolerance to the ingestion of foods rich in folic acid, suggesting that the antigenic determinants responsible for the hypersensitivity reactions are not present or are occult in natural folates but appear in the unconjugated synthetic form of the vitamin (pteroylglutamic acid).

According to our results, it seems unlikely that we are dealing with a type I immunologic mechanism. Alternative pathways, such as the direct release of mast cell mediators and complement activation, could be relevant but were not determined. Given that people in North America and other countries are receiving this vitamin in the form of mandatory folic acid–fortified food, we recommend a high degree of suspicion in every patient with chronic urticaria and a history of folic acid intake.

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ALLERGIC REACTION TO MECASERMIN

Mecasermin (Increlex; Beaufour Ipsen Inc, Paris, France), a recombinant human insulin–like growth factor I (IGF-1), was approved by the Food and Drug Administration in 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency. In studies of children with short stature treated with mecasermin, no serious allergic reactions have been reported.^{1–5} However, a recent case report described the first occurrence of anaphylaxis to mecasermin.⁶

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We report a second case of cutaneous and systemic reactions to mecasermin.

An 11-year-old boy with short stature (height, –3.9 SDs; weight, –1.7 SDs [20.3 kg]) was treated with mecasermin after failing to respond to 3 years of growth hormone treatment. Three weeks after reaching the full mecasermin dose (120 µg/kg subcutaneously twice daily), he developed urticarial lesions around the injection site (with each injection), progressing once to generalized urticaria. Mecasermin treatment was discontinued until the drug was administered under physician observation. Within minutes, the patient developed an urticarial lesion over the injection site, which was treated with oral diphenhydramine. During the following several hours, he developed urticarial lesions 10 cm in diameter (Fig 1) in several sites of previous injections, mild facial swelling, and cough. The patient remained afebrile and normotensive without tachycardia or tachypnea. The results of the physical examination were otherwise unremarkable. He was treated with oral diphenhydramine until the symptoms resolved. Mecasermin treatment was discontinued pending further evaluation.

Two months later, skin testing was performed with the diluent and mecasermin from the vial used at home, a different vial of the same lot, and a vial of a different lot. Skin prick testing was performed with dilutions of 1:100, 1:10, and full strength (10 mg/1 mL). Intradermal testing was performed with 0.02 mL of 1:100 and 1:10 dilutions. The histamine control was positive, with wheal-and-flare reactions of 3 mm and 10 mm, respectively. The results of tests with saline control, diluent, and dilutions of mecasermin were negative. Serum specific IgE antibody to mecasermin was not measured because no assay is available. Given the negative skin test results, lack of an adequate treatment response with growth hormone, and ongoing growth failure, a protocol that accomplished a rapid desensitization or a gradual dosing challenge to mecasermin was devised.

Mecasermin is injected subcutaneously starting at a range of 40 to 80 µg/kg titrated over time to 120 µg/kg twice daily. To reach an initial target dose of 80 µg/kg, four 20-µg/kg doses were administered subcutaneously every 30 minutes. Injections were rotated among the lateral aspect of the thighs and the posterior part of the upper arms and tolerated without reaction. Vital signs were monitored every 15 minutes, and rescue medications (epinephrine, ranitidine, diphenhydramine, methylprednisolone, albuterol, and isotonic sodium chloride solution) were administered at the bedside. Twelve hours after the start of administration, an 80-µg/kg dose was tolerated, except for a small bruise with mild erythema that appeared over the injection site after several hours. In another 12 hours, a second 80-µg/kg dose was given. Within 2 hours, an area of induration with warmth and erythema, but without pruritus, developed over the injection site.

To reevaluate for an IgE-mediated reaction, skin prick testing with full-strength mecasermin was performed. The histamine control was positive with wheal-and-flare reactions of 3 mm and 5 mm, respectively. The isotonic sodium chloride solution control and mecasermin tests produced negative results. Because no systemic symptoms occurred, twice daily injections were continued at home. The patient continued to have small erythematous wheals without pruritus over the injection sites. However, 3 weeks later, the patient developed angioedema of the lips 3 hours after an injection. The angioedema resolved over several hours. Mecasermin treatment was permanently discontinued.

This case is the second report of local and systemic cutaneous adverse effects of mecasermin clinically consistent with an allergic