Transient hypogammaglobulinemia and severe atopic dermatitis: Open-label treatment with immunoglobulin in a case series

Moira E. Breslin, M.D., M.Sc.,[1] Joanna H. Lin, M.D.,[2] Robert Roberts, M.D., Ph.D.,[1] Kellie J. Lim, M.D.,[3] and E. Richard Stiehm, M.D.[1]

ABSTRACT

Background: *We reported on six infants between 5 and 11 months old, with transient hypogammaglobulinemia of infancy and severe refractory atopic dermatitis, who were treated with open-label immunoglobulin (Ig) after conventional therapy failed. All six infants had an IgG level of <225 mg/dL, elevated eosinophil and IgE levels, and no urine or stool protein losses, but they did exhibit hypoalbuminemia.*

Objective: *To evaluate the utility of open-label immunoglobulin in infants with severe atopic dermatitis for whom conventional therapy failed. We reviewed the clinical utility of intravenous immunoglobulin in the treatment of severe atopic dermatitis, the most recent research in the field, and suggested mechanisms for its benefit.*

Methods: *The six infants were identified from a retrospective chart review at the University of California Los Angeles Allergy and Immunology outpatient pediatric clinic.*

Results: *All six patients were treated with 400 mg/kg/month of intravenous immunoglobulin and had normalization of their IgG and albumin levels, and all but one had clinically improved atopic dermatitis.*

Conclusion: *Infants with severe atopic dermatitis who did not respond to conventional therapy avoidance may benefit from intravenous immunoglobulin therapy.*

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We reported on six infants between 5 and 11 months old with transient hypogammaglobulinemia of infancy (THI) and severe refractory atopic dermatitis (AD) who were treated with intravenous immunoglobulin (IVIG) after conventional therapy failed. All six patients had an immunoglobulin G (IgG) level of <225 mg/dL, elevated eosinophil and IgE levels, and no urine or stool protein losses, but they did exhibit hypoalbuminemia. All the patients were treated with 400 mg/kg/month of IVIG and had normalization of their IgG and albumin levels; all but one patient had clinically improved AD. We reviewed the clinical utility of IVIG herein in the treatment of severe AD and indicated mechanisms for its benefit.

From the [1]Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, University of California Los Angeles (UCLA), Los Angeles, California, [2]McKinney Allergy and Asthma Center, McKinney, Texas, and [3]Division of Pulmonary and Critical Care Medicine, UCLA Department of Medicine, UCLA, Los Angeles, California

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Address correspondence to Moira Breslin, M.D., c/o Division Chief, Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, University of California Los Angeles, 10833 Le Conte Ave, Room 12-430 MDCC, Los Angeles, CA 90095

E-mail address: mbreslinucla@gmail.com

METHODS

The six patients were identified from a retrospective chart review at the University of California Los Angeles Allergy and Immunology outpatient pediatric clinic. Approval was obtained through the University of California Los Angeles Institutional Review Board (IRB 15–001563) and consistent with ethical guidelines for research that involves children. Procedures were in accordance with ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 1983.

The following clinical criteria were used to diagnose AD: chronically dry, itchy, inflamed skin in typical distributions (*i.e.,* flexor and extensor surfaces). No objective measure was implemented to score the severity of AD. The following criteria were used to define THI: infants >6 months old, with IgG levels two standard deviations below the mean for their age.[1] Two pediatric immunologists (R.R., E.R.S.) assessed the patients during and after treatment. IVIG infusions were provided by registered nurses at the outpatient clinic's infusion center. Criteria for initiating IVIG were decided on an individual basis and on an evaluation of the severity of the AD lesions, extent of bacterial superinfection, and degree of hypogammaglobulinemia. The patients were administered monthly IVIG infusions of 400 mg/kg. IgG levels were assessed before each administration of IVIG. The discontinuation of

IVIG was based on clinical improvement and normalization of IgG levels by age-adjusted criteria.

RESULTS

The pertinent baseline clinical and laboratory features of the patients are summarized in Table 1. Of the six patients, two were girls and four were boys. One patient was Hispanic, one was Asian, two were white, and two were of white-Asian descent. Their initial presentation of AD occurred between 1 and 4 months of age (mean, 2.6 months; median, 3 months). The mean age at presentation to the clinic was 6.7 months (range, 5–11 months). All the patients had poor responses to combination oral and topical steroids, oral antihistamines, and/or antibiotics for treatment periods of 2–8 months before our initial evaluation. There was no evidence of coarse facial features and recurrent refractory skin infections consistent with hyper-IgE syndrome in these patients, nor was there evidence of this syndrome in their family histories.

All the patients exhibited positive skin-prick test results or elevated serum-specific IgE levels to specific foods, whereas three patients (case nos. 1, 2, and 3) exhibited clinical IgE-mediated reactions (lip and facial swelling or urticarial rash) to specific foods (milk, soy, and fish). All the patients had elevated serum IgE levels (reference value, <100 IU/mL) with a mean of 4957 IU/mL, and all had serum IgG levels below normal, with a mean level of 154 mg/dL (range, 70–225 mg/dL) and median of 143 mg/dL. The eosinophil percentage was elevated (1–3%) in all the patients, with a mean absolute count of 3283/mL (range, 1900–6700/mL). The serum albumin level was decreased, with a mean of 2.5 g/dL (range, 2.0–3.0 g/dL). All the patients had normal liver function enzymes at presentation. The stool α 1-antitrypsin results in four patients (case nos. 2, 3, 5, and 6) were negative. Routine urinalysis results for three patients (case nos. 2, 5, and 7) were negative for proteinuria. Further studies, not included in this article, consisted of IgG subsets, B- and T-cell lymphocyte studies, and antibody response titers to immunizations (*Haemophilus influenzae* and *Streptococcus pneumoniae*), to rule out other immune abnormalities. The baseline clinical and laboratory characteristics of the six patients are presented in Table 1.

All of the patients had normalized and sustained IgG and albumin levels after multiple monthly treatments with IVIG. One patient (case no. 6) had a normalized IgG level, but his atopy was refractory to IVIG. As such, IVIG was discontinued, and this patient was considered to have a treatment failure. In addition, two patients (case nos. 2 and 5) developed other forms of atopy (asthma and allergic rhinitis) within a couple of years after achieving good control of their AD. Clinical results are presented in Table 2.

DISCUSSION

AD is a chronic inflammatory skin disease with hallmark dry patches, elevated serum IgE levels, and eosinophilia.[2] Infants with AD would be expected to have normal immunoglobulin and albumin levels unless they had profound malnutrition or severe AD, as in the patients we presented herein. All six patients presented had hallmark signs of AD, elevated serum IgE and eosinophil levels, and no urine or stool protein losses, but they did exhibit hypoalbuminemia. We hypothesize that, in these severe cases of AD, protein loss occurs through the skin. All six patients presented had IgG levels of <225 mg/dL, which indicated a diagnosis of THI. THI is a well-recognized immunodeficiency of infants 6 months to 4 years of age, in which serum IgG levels are persistently two standard deviations below the normal age-adjusted mean. Two groups have been proposed within the THI population: those who remain asymptomatic, and those who are symptomatic and present with recurrent sinopulmonary infections. Although the incidence of concurrent atopy and THI remains unknown,[3–5] we propose a third group, in which atopic disease is prominent. As in our institution, Dorsey and Orange[6] describe 24 children with THI who had comorbid atopic characteristics: 42% with rhinitis, 38% with food allergy, 25% with AD, and 17% with urticarial rash.

The practice parameters for primary immunodeficiency report that 10–20% of patients with THI and with severe and recurrent infections were treated with immunoglobulin while admitted to the hospital.[7] The treatment of these patients with immunoglobulin remains controversial. The most recent primary immunodeficiency practice parameters more clearly clarify the role in those patients in whom antibiotic prophylaxis failed or was not tolerated, stating that immunoglobulin replacement is to be considered as a second-line therapy during periods of respiratory infections (summary statement 108).[8] The hesitation to administer immunoglobulin treatment is that this therapy may cause a delay in the maturation of the humoral immune system because of the interference from passively transferred antibodies. The practice parameters for AD[9] are more explicit in opposition to immunoglobulin replacement and do not recommend the use of IVIG because of "conflicting results,"[10] and that "it remains unproven."[3]

We hypothesize that IVIG aids in the healing of atopic dermatitis lesions by restoring normal immunoglobulin levels. IVIG treatment leads to rapid improvement not previously observed with other therapeutic initiatives. Possible mechanisms for protective immunomodulatory effects of IVIG are included in Table 3. Of particular interest for the treatment of AD is the blockade of Fas interactions by anti-Fas antibodies in IVIG because a possible mechanism of AD is through

Table 1 **Baseline characteristics**

Patient No.	Sex	Age of AD Onset, mo	Age Evaluated, mo	IgE, IU/mL	IgG (reference range for age), mg/dL*	IgA (reference range for age), mg/dL*	IgM (reference range for age), mg/dL*	% Eosinophil Count (count/mL)	Albumin Level (2.8–5.0), g/dL	Family History	Additional Baseline Features
1	M	3	6	2246	87 (427 ± 386)	9 (21 ± 13)	27 (43 ± 17)	17 (2800)	2.5	Mother and father with allergic rhinitis	Cow's milk and soy allergy; antibody levels not obtained
2	F	2	5	309	197 (427 ± 386)	25 (21 ± 13)	77 (43 ± 17)	17 (1900)	2.5	Mother with atopic dermatitis	Failure to thrive; cow's milk, soy, egg allergies; history of *Staphylococcus aureus* bacteremia; tetanus, influenza, and *Haemophilus influenza* ab. neg.
3	F	4	6	2135	115 (427 ± 386)	<25 (21 ± 13)	38 (43 ± 17)	13 (2000)	3	Father with asthma and allergic rhinitis	Failure to thrive; goat and cow's milk allergy; *H. influenza,* tetanus and pneumococcal ab. pos.
4	M	3	5	856	164 (427 ± 386)	31 (21 ± 13)	74 (43 ± 17)	23 (4000)	2.4	Mother with allergic rhinitis	Scalp fungal and bacterial infection; cow's milk, egg, barley, oat, rice allergy; tetanus and *H. influenza* ab. neg.; influenza ab. pos.
5	M	1	7	11,492	70 (661 ± 119)	14 (37 ± 18)	21 (54 ± 23)	24 (6700)	2.5	Mother and father with atopic dermatitis	Failure to thrive; egg, corn, cow's milk allergy; *H. influenza,* tetanus ab. neg.; Diphtheria ab. pos.
6	M	3	11	12,706	225 (661 ± 119)	29 (37 ± 18)	<20 (54 ± 23)	14 (2300)	2	Mat. uncle with food allergy, mat. aunt with allergic rhinitis, pat. grandfather with food allergies	Peripheral edema; serum electrolyte imbalance; egg, cow's milk, peanut, tree nut allergy; immunization refusal; *H. influenza* ab. neg.

AD = Atopic dermatitis; IgE = immunoglobulin E; ab. = antibody; pos. = positive; neg. = negative; mat. = maternal; pat. = paternal.
**From Ref. 1.*

Table 2 **Clinical outcomes**

Case No.	IVIG, mo	IgG Levels after IVIG, mg/dL	AD after IVIG	Other	Current Status
1	4	889	Improved	Outgrew soy allergy; developed peanut, tree nut, shellfish, and fish allergies; developed allergic rhinitis	10 years old; last seen in the A&I clinic on Jul 5, 2012, with dry patches on ankles
2	3	534	Improved	Developed allergic rhinitis	10 years old; last seen in the A&I clinic on Mar 4, 2005, with dry skin and lichenified patches on antecubital fossae and extremities
3	11	607	Improved	Developed sesame, legume allergies	11 years old; last seen in the A&I clinic on Aug 4, 2006, with mild AD of the cheeks, elbows, shoulder, knees
4	5	810	Improved		14 years old; lost to follow-up, last seen in emergency department on Jun 1, 2003, with cellulitis of elbow and cheek
5	18	900	Resolved	Developed asthma, allergic rhinitis, FA	18 years old; last seen in the A&I clinic on Dec 18, 2009; skin clear
6	7	677	Persistently severe	Persistent dairy and egg allergies, developed wheat allergy	10 year old; last seen in the A&I clinic on Jan 21, 2015; severely excoriated, erythematous, dry areas on the arms, legs, trunk, and face

IVIG= Intravenous immunoglobulin; IgG = immunoglobulin G; AD = atopic dermatitis; A&I = allergy and immunology; FA = food allergy.

Table 3 **Immunologic effects of intravenous immunoglobulin G**

1. Inhibits antibody synthesis by direct effect on proliferating B cells
2. Contains anti-idiotypic antibodies, which can combine with autoimmune antibodies and remove them rapidly from circulation
3. Combines with Fc receptors, which causes an Fc receptor blockade, reduces destruction of antibody-coated cells in the spleen and liver
4. Combines with other cell surface receptors to inhibit cellular activation; prevents Fas-mediated cell death of keratinocytes by blocking the Fas receptor
5. Downregulates immune activation by decreasing inflammatory cytokine release or action
6. Neutralizes bacterial superantigens and prevents them from activating T cells
7. Combines with complement components to prevent complement-mediated tissue injury
8. Neutralizes viral or bacterial antigens that may trigger or cause the disease

T-cell–mediated Fas-induced keratinocyte apoptosis. Further mechanistic studies would be helpful in elucidating this pathway.

For the proposed third group with AD, guidelines for standardized treatment of severe AD in the setting of THI do not exist. However, a recently published randomized control trial of children with severe AD and hypogammaglobulinemia treated with immunoglobulin showed promising, although transient, results.[11] Other investigators also showed improvement in their patients with AD after they received regular IVIG.[4,5,11] Another report, of five children, ages 7 to 12 months, who received IVIG (2 g/kg/dose) monthly for three doses had improved skin findings and significantly decreased inflammatory markers (ICAM-1, ELAM-1, ECP, and IL-2R).[12] Perhaps most compelling was the randomized, placebo-controlled study of 40 children with moderate-to-severe AD who were treated with higher doses of IVIG (2.0 g/kg IVIG), which showed that 3 months of therapy led to clinical improvement, although results declined after 6 months of treatment.

CONCLUSION

Given the small sample size, the nature of an open-label, uncontrolled case series, it is not possible to generalize these findings. However, these findings indicated that restoring normal immunoglobulin levels improved severe AD in patients with THI. We suggest that infants with severe AD, especially those who have recurrent skin infections, should be evaluated for possible hypogammaglobulinemia and, as such, a diagnosis of THI. We acknowledge that the diagnosis of THI is one of exclusion and is often delayed until the recovery of antibody production occurs months to years after it is suspected clinically. Despite this challenge, the benefits of IVIG in the setting of protein loss secondary to skin barrier breakdown in infants with severe AD should be considered, especially given that in severe cases of hypoproteinemia, there is a risk of hypovolemic shock. Thus, even before THI is confirmed, infants with severe AD who do not respond to standard treatment with corticosteroids, antibiotics, and appropriate allergen avoidance may benefit from IVIG therapy.

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