

Letter to the Editor

High-dose cyclophosphamide used to treat aplastic anemia in a patient with respiratory and food allergies has a prolonged effect on serum IgE levels

To the Editor:

Food allergy is an increasingly common medical problem with no treatment available other than avoidance. Novel therapeutic strategies under investigation in research trials include anti-IgE antibodies, oral and sublingual therapy, and modified vaccines.^{1,2} In this case report, we followed a patient with a history of rhinitis, asthma, and severe, persistent cow's milk allergy who developed aplastic anemia that was treated with high-dose cyclophosphamide (HiCy).

The patient was diagnosed with severe milk and beef allergy as an infant. Over the years, he experienced multiple anaphylactic reactions with minute accidental ingestions of milk. He later outgrew the beef allergy, but the milk allergy persisted. He also developed allergic rhinitis and asthma. He did well as long as he practiced strict avoidance of all milk products. He otherwise tolerated a regular diet including peanut, tree nuts, shellfish, fish, wheat, soy, and egg.

He was in his usual state of health until age 19 years when he developed bleeding gums after a streptococcal-like throat infection with fatigue and syncope. On admission, a complete blood cell count showed a hemoglobin level of 3.5 g/dL, platelet count of 8000 K/cu mm, white blood cell count of 500 cells/cu mm, and an absolute neutrophil count of 190. He was transfused with packed red cells and platelets. A bone marrow biopsy showed markedly hypocellular marrow with scattered erythroid islands, lymphocytes, and plasma cells, but no myeloid elements were identified and he was diagnosed with acquired severe aplastic anemia. An HLA-matched donor was not available, and HiCy treatment was initiated in mid-December 2009. His course was complicated with neutropenic fever, but he otherwise tolerated HiCy very well and his aplastic anemia is currently in remission.

In March 2010, he had an accidental ingestion of milk with 1 bite of a chocolate chip cookie. Within minutes, he developed oral pruritus, shortness of breath, and facial urticaria. He was treated with epinephrine and corticosteroids. In July 2010, he had another accidental ingestion with a single bite of a cheese omelet. Within minutes, he developed oral pruritus, facial urticaria, and shortness of breath. He was treated with epinephrine and diphenhydramine. In January 2011, he ate a shrimp stir-fry dish at a Thai restaurant that was presumed milk free, but possibly contaminated with peanuts and developed facial urticaria, oral pruritus, and shortness of breath consistent with prior allergic reactions. He continues to strictly avoid milk, but eats peanuts 1 time per month, tree nuts 2 times per month, and shellfish rarely because of self-preference without any reactions.

Tables I and II provide a summary of various immunoglobulin measurements, some dating back to 2003, at which time the milk-specific IgE level, as measured by ImmunoCap assay, was 42.6 kU/L. This rose to 220 kU/L and peaked at 310 kU/L at the time of his aplastic anemia diagnosis in December 2009. At that time he had low-to-moderate levels of cat-, dog-, and dust mite-specific IgE, a very low and clinically insignificant level of egg white-specific IgE, and undetectable IgE to soybean and peanut. Subsequent laboratory values at approximately 3 months and 6 months after HiCy treatment revealed about a 40% to 50% decline

TABLE I. Values for various immunoglobulin levels before and after HiCy administration

Time relative to HiCy treatment	Total serum IgG (mg/dL)	Total serum IgA (mg/dL)	Total serum IgM (mg/dL)	Total serum IgE (kU/L)	Total IgE % of 12/3/09 value
-5.7 y	ND	ND	ND	ND	ND
-8 mo	ND	ND	ND	ND	ND
-1 wk	1060	152	102	679.2	100
+2.5 mo	632	69	22	45.8	6.7
+6 mo	522	56	27	21.4	3.2
+13 mo	565	64	60	183	26.9
+19 mo	ND	ND	ND	96	14.1

ND, Not determined.

in total IgG and IgA levels along with an 80% decline in the IgM level as well as a near-95% decline in total milk-specific IgE level. Low levels of IgE to egg white and dust mite became undetectable, while dog- and cat-specific IgE level declined by 80% to 90%. Indeed, dog-specific IgE became undetectable about 6 months after treatment, and cat-specific IgE remained barely detectable.

At 1 year following treatment with HiCy, IgM levels were starting to return and total IgE levels rebounded to about 25% of pretreatment baseline. However, IgE to cow's milk remained at 5% of pretreatment levels, whereas dust mite IgE levels had returned to baseline, and cat and dog IgE levels were increasing but still markedly depressed. New specificities of IgE to egg white, peanut, and soybean appeared. At 18 months post-HiCy treatment, the total IgE level declined further to 14% of pretreatment baseline, with cow's milk, egg white, and peanut IgE persisting, but at levels lower than at 12 months, and soybean IgE increasing slightly, albeit at low levels. Also declining slightly compared to levels at 12 months was specific IgE to dust mite, cat, and dog. Thus, by 18 months after HiCy treatment, levels of pre-existing total IgE, cow's milk, dog, and cat IgE remained remarkably reduced by 85% to 97%, while IgE production to egg increased or remained relatively unchanged to dust mites. During the same time period, new IgE recognizing soybean and peanut appeared and persisted. In short, the HiCy treatment appears to have reset his IgE responses to a variety of allergens. He continues to eat egg and soy, but continues to avoid milk and peanut, the latter because of dietary preference.

HiCy (200 mg/kg over 4 days) was initially developed as a conditioning regimen for allogeneic bone marrow transplantation. Recently, HiCy without bone marrow transplantation has been used as a method to induce remission in severe aplastic anemia and other autoimmune disorders.^{3,4} HiCy is highly immunosuppressive, but not myeloablative. Early hematopoietic progenitors, including stem cells, are relatively resistant to HiCy because of their high levels of aldehyde dehydrogenase. However, T cells, B cells, and natural killer cells are exquisitely sensitive to HiCy because of their relatively low levels of aldehyde dehydrogenase.⁵ Relatively little is known about the sensitivity of plasma cells, although there is 1 report that cyclophosphamide preferentially affects IgE over all other isotypes of antibodies, consistent with our findings.⁶ Cyclophosphamide is well known to affect T_H1-mediated disease, but limited data exist for allergic diseases. Interestingly, in our patient, several specific IgEs became undetectable, yet presumably because of the extremely high pretreatment level of milk-specific IgE, this did not abate, and even

Time relative to HiCy treatment	Cow's milk		Egg white		Peanut		Soybean		Cat dander		Dog dander		Der pter IgE %		Der f IgE %	
	Cow's milk IgE (kU/L)	Cow's milk IgE % of 12/3/09 value	Egg white IgE (kU/L)	Egg white IgE % of 12/3/09 value	Peanut IgE (kU/L)	Peanut IgE % of 12/3/09 value	Soybean IgE (kU/L)	Soybean IgE % of 12/3/09 value	Cat dander IgE (kU/L)	Cat dander IgE % of 12/3/09 value	Dog dander IgE (kU/L)	Dog dander IgE % of 12/3/09 value	Der pter IgE (kU/L)	Der pter IgE % of 12/3/09 value	Der f IgE (kU/L)	Der f IgE % of 12/3/09 value
-5.7 y	42.6		ND		ND		ND		ND		ND		ND		ND	
-8 mo	220		ND		ND		ND		ND		ND		ND		ND	
-1 wk	310	100	0.26	100	<0.1	<0.1	<0.1	<0.1	2.2	100	22.5	100	0.61	100	0.43	100
+2.5 mo	21.4	6.9	<0.1	0	<0.1	<0.1	<0.1	<0.1	0.8	36.4	2.21	10	<0.1	0	<0.1	0
+6 mo	12.6	4.1	<0.1	0	<0.1	<0.1	<0.1	<0.1	0.22	10.0	<0.1	0	<0.1	0	<0.1	0
+13 mo	13.3	4.3	1.58	608	4.02	4020*	0.33	330*	0.44	20.0	1.41	6	0.69	113	0.41	95
+19 mo	8.52	2.7	1.34	515	3.68	3680*	0.42	420*	0.23	10.5	1.24	6	0.53	87	0.16	37

VD, Not determined.

*A pretreatment value of 0.1 kU/L was used for these calculations.

after HiCy he continued to have food-related anaphylaxis to milk. Although HiCy may reduce total and specific IgE levels for at least 12 months, it may also reset IgE production. Indeed, our patient developed new IgE sensitizations, albeit of unclear clinical significance. Whether the persistence of clinical reactivity is due primarily to the residual amount of remaining milk-specific IgE being produced by long-lived plasma cells,⁷ IgE production and its persistence in the mucosa,⁸ effects on regulatory T cells⁹ or other factors less affected by HiCy cannot be determined.

In conclusion, to our knowledge, this is the first case that demonstrates the effect of HiCy on IgE levels in an individual with food and respiratory allergies and demonstrates prolonged and marked suppressive effects on some pre-existing IgE levels along with the appearance of new IgE specificities. At least for milk, his clinical reactivity remained unchanged based on accidental exposures, clearly demonstrating a disconnect between IgE levels and clinical reactivity. How long these changes will persist, and their long-term clinical relevance, remains to be seen.

Marisha L. Cook, MD^a
Robert A. Brodsky, MD^b
Robert Hamilton, PhD^a
Robert A. Wood, MD^c
Bruce S. Bochner, MD^a

From the Divisions of ^aAllergy and Clinical Immunology, ^bHematology, and ^cPediatric Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore, Md. E-mail: bbochner@jhmi.edu.

Disclosure of potential conflict of interest: R. A. Brodsky has received consultancy fees from Alexion Pharmaceuticals and has received research support from the National Institutes of Health (NIH) and Tedco. R. A. Wood has received consultancy fees from the Asthma and Allergy Foundation of America, is employed by Johns Hopkins University, has received research support from the NIH, and receives royalties from UpToDate. B. S. Bochner is on the Allakos and Merck scientific advisory boards; has received consultancy fees from TEVA, Sanofi-Aventis, United States Diagnostic Standards, Medicis, Pharmacyclics, Hoffman-La Roche, and Tarsa Therapeutics; is employed by Johns Hopkins University; has received research support from the NIH and the Dana Foundation; has a patent through Johns Hopkins on Siglec-8-related patents; receives royalties from Elsevier and UpToDate; and has stock/stock options in Allakos and Glycomimetrics, Inc. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Kim EH, Burks W. Managing food allergy in childhood. *Curr Opin Pediatr* 2012;24: 615-20.
2. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. *J Allergy Clin Immunol* 2012;129:906-20.
3. Brodsky RA, Chen AR, Dorr D, Fuchs EJ, Huff CA, Luznik L, et al. High-dose cyclophosphamide for severe aplastic anemia: long-term follow-up. *Blood* 2010;115: 2136-41.
4. Drachman DB, Adams RN, Hu R, Jones RJ, Brodsky RA. Rebooting the immune system with high-dose cyclophosphamide for treatment of refractory myasthenia gravis. *Ann N Y Acad Sci* 2008;1132:305-14.
5. Brodsky RA. High-dose cyclophosphamide for autoimmunity and alloimmunity. *Immunol Res* 2010;47:179-84.
6. de Macedo MS, Mota I. Antigenic competition in IgE antibody production, II: effect of cyclophosphamide. *Immunology* 1982;47:67-74.
7. Luger EO, Fokuhl V, Wegmann M, Abram M, Tillack K, Achatz G, et al. Induction of long-lived allergen-specific plasma cells by mucosal allergen challenge. *J Allergy Clin Immunol* 2009;124:819-26.e4.
8. Dullaers M, De Bruyne R, Ramadani F, Gould HJ, Gevaert P, Lambrecht BN. The who, where, and when of IgE in allergic airway disease. *J Allergy Clin Immunol* 2012;129:635-45.
9. Ghiringhelli F, Larmonier N, Schmitt E, Parcellier A, Cathelin D, Garrido C, et al. CD4+CD25+ regulatory T cells suppress tumor immunity but are sensitive to cyclophosphamide which allows immunotherapy of established tumors to be curative. *Eur J Immunol* 2004;34:336-44.