

## Letter to the Editor

**Induction of remission of idiopathic anaphylaxis with rituximab**

*To the Editor:*

Idiopathic anaphylaxis (IA) is a life-threatening disease characterized by episodes of anaphylaxis without a recognizable specific trigger, when other possible diagnoses have been ruled out.<sup>1,2</sup> It is more common in adults than children and in women than men, and up to one-half of affected patients are atopic.<sup>3,4</sup> IA is by definition a diagnosis of exclusion that requires extensive evaluation by experienced allergists to rule out hidden allergens and alternative conditions. Frequent IA is defined as at least 2 episodes in the preceding 2 months or at least 6 episodes in a year.<sup>1</sup> Immediate treatment, as in other types of anaphylaxis, is based on prompt administration of intramuscular epinephrine. Although there is no standardized long-term treatment, oral corticosteroids combined with antihistamines may reduce the frequency and severity of episodes.<sup>2</sup> However, due to this condition's rarity, no randomized, controlled treatment trials have been performed. Few studies have provided insight into the pathogenesis of IA. Patients with acute IA have higher levels of circulating activated T cells than IA patients in remission and controls.<sup>5</sup> In addition, both patients with acute IA and in remission have a significantly higher percentage of activated B cells than controls, suggesting a prominent role of B cells in the pathogenesis of this disease.<sup>5</sup> We report a patient with frequent refractory IA who had complete remission after treatment with rituximab, a chimeric anti-CD20 monoclonal antibody that targets and depletes circulating B cells.

The patient is a 17-year-old girl with asthma and allergic rhinitis who developed mild, chronic urticaria and frequent episodes of anaphylaxis characterized by sudden-onset pruritus, erythema, hives, abdominal pain, diarrhea, throat-tightness, stridor, and wheezing. Anaphylaxis occurred every 3 to 30 days during 16 months, presenting spontaneously or after eating, with no specific food or other recognizable triggers, such as medications, exercise, or menses. Family history was notable for a 3-year history of severe chronic urticaria in the patient's mother that remitted with mycophenolate mofetil, and episodes of acute angioedema after ingestion of alcohol-containing beverages in her father. Several episodes were witnessed and confirmed by experienced allergists, and all episodes were promptly relieved by intramuscular epinephrine. Laboratory studies showed an elevated total IgE of 518 IU/mL; skin prick test (SPT) results that were positive to tomato (5 mm) and wheat, carrot, and walnut (4 mm each); and low levels of serum-specific IgE to multiple foods. However, multiple open food allergen challenges to suspicious or SPT/IgE-positive foods were negative, and the patient had several episodes after eating foods that had tested negative on SPTs and specific IgE. Hidden allergens—such as spices, contaminants, and delayed reactions to mammalian meat—were ruled out by history, and double-blind placebo-controlled food allergen challenge to the food preservative butylated hydroxytoluene also showed negative results. Progesterone hypersensitivity was ruled out clinically, because of the persistence of episodes after discontinuation of oral contraceptives and the absence of association of IA episodes to the menstrual cycle. Systemic mastocytosis, monoclonal mast

cell activation syndromes, hereditary angioedema, and carcinoid were ruled out (Table I). The patient's condition failed to respond to combinations of high dose H<sub>1</sub> and H<sub>2</sub> antihistamines, a leukotriene receptor antagonist, systemic corticosteroids up to 1 mg/kg daily, mycophenolate mofetil up to 2 g daily, and an elimination diet restricted to only 3 ingredients to which she had normal specific IgE and SPT. An 8-month treatment with omalizumab 300 mg every 2 weeks only transiently made episodes less frequent, but then she continued with weekly episodes during and after this treatment.

Given the high frequency of anaphylaxis and earlier reports of response to rituximab in patients with chronic urticaria, treatment with this biological therapy was initiated. Rituximab was administered in 2 doses of 1000 mg given intravenously 14 days apart, as in standard protocol for autoimmune conditions at our institution. The patient ceased to have anaphylaxis and urticaria 10 days after the second dose (Fig 1). While her B-cell count remained at 0 cells/mm<sup>3</sup>, she had no new episodes of anaphylaxis or symptoms of chronic urticaria. After 9 months, B-cell count normalized (132 cells/mm<sup>3</sup>), and the patient again began having skin pruritus, intermittent hives, and anaphylaxis every 3 to 7 days. Retreatment with 2 doses of rituximab 500 mg 14 days apart was chosen, to reduce costs. This led again to full remission of anaphylaxis. After 10 months of follow-up since the last episode of anaphylaxis, the patient has continued to receive rituximab 1000 mg every 6 months and fexofenadine 180 mg daily, remaining asymptomatic on a normal diet. The latter drug was maintained for allergic rhinitis. Her highest B-cell count during this anaphylaxis-free period was 63 cells/mm<sup>3</sup> before the most recent rituximab dose. The patient has not had any serious infections or other adverse events during follow-up, except for a mild decrease in IgM (Table I). Notably, total IgE has gradually decreased to 159 IU/mL.

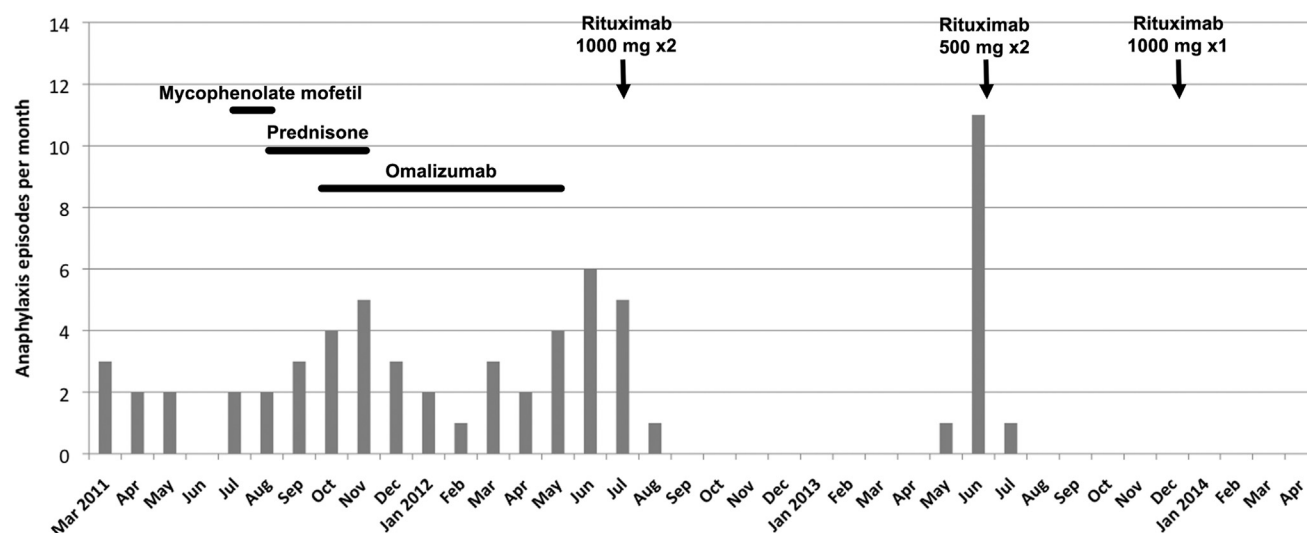
To our knowledge, this is the first report of successful treatment of IA with rituximab. Long-term treatment of IA is often frustrating, due to the lack of standardized treatments and to the life-threatening nature of treatment failures. Most treatment evidence is based on case reports and observational series.<sup>3,4</sup> First-line treatments usually include antihistamines, glucocorticoids, or both. Up to 20% of patients with frequent IA are reported to be glucocorticoid-dependent, and sometimes the label "malignant IA" is used to identify severe IA that is resistant to standard treatment.<sup>1</sup> Promising results have been observed in several patients with the use of omalizumab.<sup>6</sup> However, our patient experienced treatment failure with this medication as well.

Rituximab is commonly used in the treatment of B-cell malignancies and autoimmune diseases, but its use in allergic diseases is rare. Reports have documented the successful use of rituximab in chronic autoimmune urticaria, a disease mediated by pathogenic IgG autoantibodies against FcεRIα or IgE.<sup>7,8</sup> Thus, depletion of B-cell producing IgG antibodies may mediate a decrease in pathogenic autoantibodies and improvement in clinical symptoms. However, one previous report documented lack of response to rituximab in chronic urticaria.<sup>9</sup> Rituximab has also been used in drug desensitization protocols of patients with hemophilia B and anaphylaxis to factor IX concentrates.<sup>10</sup> In these cases, success has been attributed to eradication of high affinity antibodies against factor IX, although it is still

**TABLE I.** Laboratory and imaging test results at baseline and after 21 months of follow-up after initial rituximab treatment

| Test                                                                           | Baseline                                                          | Follow-up |
|--------------------------------------------------------------------------------|-------------------------------------------------------------------|-----------|
| IgG, mg/dL                                                                     | 1030                                                              | 1090      |
| IgA, mg/dL                                                                     | 250                                                               | 301       |
| IgM, mg/dL                                                                     | 60                                                                | 26        |
| IgE, IU/mL                                                                     | 518                                                               | 159       |
| Skin prick tests to foods (mm greater than negative control)                   | 5 mm tomato; 4 mm wheat, carrot and walnut;<br>all other negative |           |
| Specific IgE to multiple foods (ImmunoCAP; Phadia, Uppsala, Sweden)            | Negative or class I/II                                            |           |
| Multiple open food allergen challenges to suspicious or SPT/IgE-positive foods | Negative                                                          |           |
| Double-blind, placebo-controlled allergen challenge to food preservative BHT   | Negative                                                          |           |
| Total baseline tryptase                                                        | 1.7 ng/mL                                                         |           |
| Free tryptase (Medical College of Virginia, Richmond, Va)                      | <1 ng/mL                                                          |           |
| Total tryptase 2 hours after IA episode                                        | 2.11 ng/mL                                                        |           |
| D816V <i>c-Kit</i> mutation                                                    | Negative                                                          |           |
| Histopathology of suspicious skin nevi, bone marrow, and stomach               | Normal; no evidence of local or systemic mastocytosis             |           |
| C1 esterase inhibitor                                                          | Normal level and function                                         |           |
| Whole body Ga-68 DOTATATE PET/CT scan                                          | No evidence of cancer or carcinoid                                |           |
| Intrplatelet serotonin                                                         | Normal (321 ng/10 <sup>9</sup> platelets)                         |           |

BHT, Butylated hydroxytoluene; PET/CT, positron emission tomography/computed tomography.

**FIG 1.** Timeline of idiopathic anaphylaxis episodes and response to treatments.

controversial whether reactions to factor IX are IgE- or IgG-mediated. Anaphylaxis can be IgE- or IgG-mediated. Thus, possible mechanisms of rituximab in IA include depletion of putative pathogenic IgG autoantibodies or depletion of circulating total or specific IgE, as measured in our patient. The absence of a known autoantibody involved in our patient's IA makes it difficult to confirm IgG autoantibody depletion as a potential mechanism of rituximab's effectiveness in this case. A cellular effect of depleting activated circulating B cells that are increased in IA may also be postulated, and this could affect B cell–mast cell/basophil crosstalk or B cell–T cell interactions, as activated T cells are also increased in acute IA and may participate in its pathogenesis.<sup>5</sup>

Our case suggests that B-cell depletion with rituximab is a novel, highly effective treatment for IA. Further insight on the role of B cells and IgG and IgE antibodies in IA may provide clues about the mechanisms through which rituximab can induce remission of IA and potentially other allergic diseases. Additional

studies are necessary to confirm the efficacy and safety of this treatment approach in IA and standardize dosing protocols.

Arturo Borzutzky, MD<sup>a,b</sup>

Pamela S. Morales, MD<sup>a</sup>

Verónica Mezzano, MD<sup>c</sup>

Sofía Nussbaum<sup>a</sup>

A. Wesley Burks, MD<sup>d</sup>

From <sup>a</sup>the Immunology, Allergy and Rheumatology Unit, Division of Pediatrics, <sup>b</sup>the Millennium Institute on Immunology and Immunotherapy, and <sup>c</sup>the Department of Rheumatology and Clinical Immunology at the School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile; and <sup>d</sup>the Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, NC. E-mail: arturobor@med.puc.cl.

Disclosure of potential conflicts of interest: A. Borzutzky has been a speaker for Roche and Novartis Laboratories (Chile); has received research support from Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT grant nos. 1130615 and 1130387) (Chile) and FONIS (grant no. SA13I20173) (Chile); has received lecture fees from Roche Laboratories (Chile) and Pfizer (Chile); and has received travel support from Pfizer (Chile) and Abbott Laboratories (Chile). V. Mezzano has

received lecture fees from Bristol-Myers Squibb and has received support for travel, accommodations, and meeting registration from Janssen. A. W. Burks is or has been on the board for Food Allergy Research and Education, the American Academy of Allergy, Asthma & Immunology, and the Food Allergy Initiative; has received consultancy fees from Dynavax Technologies Corp, Genalyte, GLG Research, Perrigo Company, Regeneron Pharmaceuticals, Perosphere Inc, Dow AgroSciences, ExploraMed Development, McNeil Nutritionals, Merck, Nordic Biotech, Novartis Pharma AG, Nutricia North American, Portola Pharmaceuticals, Publicis Healthcare Communications Group, and Unilever; has received research support from Hycor Biomedical; has received lecture fees from Abbott Laboratories, the American College of Allergy, Asthma, and Immunology, and Mylan Speciality; has received royalties from UpToDate; has received payment for development of educational presentations from Levine Children's Hospital and Oak Ridge Associated Universities; and has stock/stock options in Allertein and MastCell Pharmaceuticals. The rest of the authors declare that they have no relevant conflicts of interest.

## REFERENCES

1. Greenberger PA. Idiopathic anaphylaxis. *Immunol Allergy Clin North Am* 2007; 27:273-93, vii-viii.
2. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010;126:477-80, e1-42.
3. Ditto AM, Harris KE, Krasnick J, Miller MA, Patterson R. Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy Asthma Immunol* 1996;77:285-91.
4. Tejedor Alonso MA, Sastre DJ, Sanchez-Hernandez JJ, Perez FC, de la Hoz Caballer B. Idiopathic anaphylaxis: a descriptive study of 81 patients in Spain. *Ann Allergy Asthma Immunol* 2002;88:313-8.
5. Grammer LC, Shaughnessy MA, Harris KE, Goolsby CL. Lymphocyte subsets and activation markers in patients with acute episodes of idiopathic anaphylaxis. *Ann Allergy Asthma Immunol* 2000;85:368-71.
6. Warrior P, Casale TB. Omalizumab in idiopathic anaphylaxis. *Ann Allergy Asthma Immunol* 2009;102:257-8.
7. Arkwright PD. Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria. *J Allergy Clin Immunol* 2009;123:510-1; author reply 1.
8. Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. *J Allergy Clin Immunol* 2011;128:1354-5.
9. Mallipeddi R, Grattan CE. Lack of response of severe steroid-dependent chronic urticaria to rituximab. *Clin Exp Dermatol* 2007;32:333-4.
10. Gamerman S, Singh AM, Makhija M, Sharathkumar A. Successful eradication of inhibitor in a patient with severe haemophilia B and anaphylaxis to factor IX concentrates: is there a role for Rituximab and desensitization therapy? *Haemophilia* 2013;19:e382-5.

<http://dx.doi.org/10.1016/j.jaci.2014.05.032>