

Letter

IgE-dependent mechanism and successful desensitization of erythritol allergy

Erythritol, a 4-carbon sugar alcohol, is widely used as a food and drug additive because of its chemical inertness, sweetness, and nontoxic nature. It is also contained in natural foods, such as fruits and mushrooms, and fermented foods, such as soy sauce.¹ We previously described a female patient who experienced many episodes of anaphylaxis; she was diagnosed as having an erythritol allergy using a skin prick test, basophil activation test (BAT) using the CD203c expression, and oral food challenge (OFC).² However, the underlying immunologic mechanism of erythritol allergy was not fully elucidated.

We administered oral immunotherapy (OIT) because the patient experienced repeated, unexpected episodes of severe anaphylaxis after the diagnosis. The ingestion of 0.3 g of 99% erythritol (Pal Sweet calorie zero) in the OFC provoked multiple urticaria and a runny nose in the patient. Subsequently, we performed OIT with a starting dose of 0.1 g with daily administration of montelukast and epinastine. At the start of the OIT, the patient was admitted to our hospital for 3 days to introduce the antigen (rush phase of OIT), which allowed her to tolerate 0.5 g of 99% erythritol at discharge. We instructed the patient to increase the daily dose by 0.1 g when she could ingest the dose without any symptoms on 14 consecutive days. However, the actual dose escalation needed to be sustained because she sometimes had an allergic symptom after an intake (Fig 1). Daily montelukast and epinastine administration was continued throughout the OIT. Although urticaria occasionally developed, especially just after increasing the antigen dose, severe symptoms, such as respiratory symptoms, did not develop throughout the OIT.

After 1 year of OIT, the patient achieved a maintenance dose of 1.8 g, which is a common 1-serving dose of 99% erythritol in a cup of coffee. However, she still occasionally experienced urticaria, especially after self-judged discontinuation of ingesting antigen. After 2 years, she continued the maintenance dose without any symptoms for 4 months. We then performed an OFC (second OFC) after 2 weeks of complete avoidance of the antigen to evaluate tolerance. The result was positive, with induction of systemic urticaria after ingesting a total of 1.8 g of 99% erythritol. After the second OFC, the patient was instructed to reintroduce and increase daily ingestion of the antigen without taking montelukast or epinastine. She was subsequently able to ingest 1.8 g of 99% erythritol without any allergic symptoms. She has been free of unexpected anaphylaxis since we started OIT.

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We also investigated IgE reactivity using the BAT. A commercial kit (Allergen Kit; Beckman Coulter, Fullerton, California) was used to quantify the basophil CD203c expression. After starting OIT, the BAT was measured every 6 months, with temporary cessation of intake and medication at least 100 hours before examination. The proportion of CD203c^{high}-positive basophils revealed no remarkable change after stimulation with 2 mg/mL of erythritol, which was 15.5% just before OIT, and remained positive (13.1%) just before the second OFC (24 months after starting OIT) (Fig 1).

We attempted to confirm the activation of basophils mediated by specific IgE to the antigen because basophils can be activated by nonspecific IgE-mediated mechanisms. For this purpose, we removed the plasma from whole blood cells by washing with phosphate-buffered saline and/or performed wortmannin pretreatment in the final BAT study. Wortmannin is a potent and specific inhibitor of phosphoinositide 3-kinase, which is activated through cross-linking of IgE on high-affinity IgE receptors. Phosphoinositide 3-kinase induces phosphorylation and activation of phospholipase and increases intracellular free calcium and histamine release.^{3,4}

Pretreatment with wortmannin inhibited basophil activation induced by anti-IgE and erythritol; however, no change was observed when *N*-formylmethionyl-leucyl-phenylalanine was used as a basophil stimulator. This result indicates that basophil activation was induced by specific IgE to erythritol. Furthermore, stimulation of washed blood cells from EDTA-treated blood with erythritol revealed a lower percentage of CD203c^{high}-positive basophils, which was not observed when they were stimulated with *N*-formylmethionyl-leucyl-phenylalanine and anti-IgE (eFig 1). This result indicates that some substances in the plasma assisted the allergic reactions caused by erythritol in vitro. These findings were compatible with our previous report in which surface IgE-removed basophils revealed reduced CD203c-expressing cells, whereas supplementation of the autologous plasma ameliorated the CD203c expression.²

Sreenath et al⁵ successfully generated an IgG antibody specific to erythritol. They conjugated erythritol to bovine serum albumin by reductive amination and immunized rabbits to generate antisera to erythritol. Recently, Venkatesh⁶ reported the possibility of generating specific IgE to erythritol. Although we failed to identify specific IgE to erythritol, an allergic reaction to erythritol might be mediated by IgE and some substance in the plasma, such as serum albumin as a carrier protein.

Erythritol has been used in Japan since 1990, and it is now used in many countries. After the first report of erythritol allergy by Yunginger et al⁷ in 2001, several cases have been reported.^{2,8} Although OIT has been attempted for various kinds of IgE-

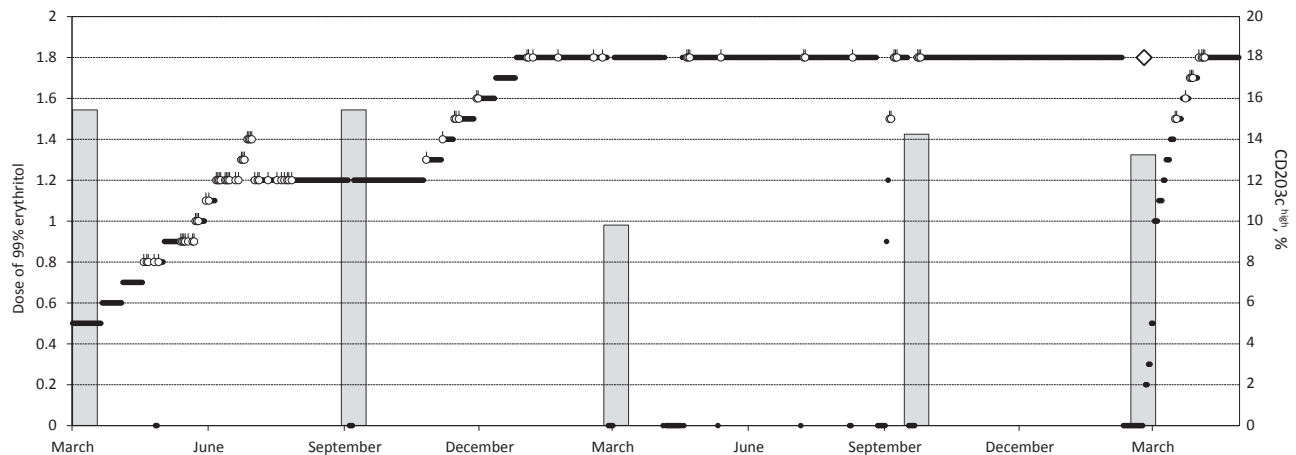


Figure 1. Time course of oral immunotherapy and the result of the basophil activation test. Black circles indicate ingestions of erythritol without symptoms, whereas white circles with bars indicate those with the development of urticaria. Gray bars indicate the results of the basophil activation test stimulated with erythritol (2 mg/mL) expressed as the proportion of CD203c^{high}-positive basophils. The white diamond indicates the result of the second oral food challenge, which induced systemic urticaria.

mediated food allergies to egg, milk, and peanuts,⁹ to the best of our knowledge, this is the first report of OIT for erythritol. We carefully discussed the limitations of OIT with the patient and her family, and the patient decided to undergo OIT to prevent unexpected anaphylaxis. As a result, she achieved temporary desensitization, but not tolerance, after 2 years of treatment. OIT could be a choice for the management of allergy to erythritol to improve the safety and quality of life of the patient.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.06.019>.

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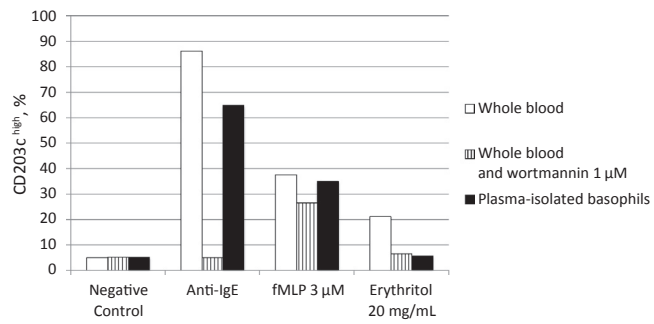
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eFigure 1. The result of the modified BAT. The proportion of CD203c^{high}-positive basophils is shown.