

with an *IL4R* single nucleotide polymorphism, although we did not.³ We agree that there might be several reasons why our relatively small study did not find an association, including small sample size and different allele frequencies of the control subjects between countries. Therefore additional research is needed before a definitive conclusion can be made about the generalizability of Guéant et al's results to non-Italian populations.

Our limited resources did not allow us to include *IL13* polymorphisms, and our emphasis was a little different: identifying both clinical and genetic risk factors and examining the importance of genetic risk factors relative to those clinical risk factors. We agree it would be informative to study *IL4* and *IL13* gene pathway interactions. The products of these 2 genes, closely located on chromosome 5, both use the IL-4 receptor α . Thus an interaction between *IL4* or *IL13* and *IL4RA* would support the role of IgE in drug allergy. Nonetheless, for gene-gene interaction studies, a very large sample size is needed to obtain reliable results. We also call attention to the marginal association of a single nucleotide polymorphism from another gene: the β -lactamase gene (*LACTB*) was marginally associated, lending support to the other aspect of our theory that penicillin is multifactorial with contributions from several genes (the *IL4* pathway but also others) and the environment (exposure to antibiotics).

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Supported by the Agency for Healthcare Research and Quality Centers for Education and Research on Therapeutics Cooperative Agreement (HS10399); the National Heart, Lung, and Blood Institute (HL K23 04337-01, to A.J.A.); and the National Institutes of Health (P20RR02074).

Disclosure of potential conflict of interest: T. Rebbeck has received research funding from and served in an advisory capacity for the National Institutes of Health and has served in an editorial capacity for the American Association for Cancer Research. The rest of the authors have declared that they have no conflict of interest.

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Available online January 5, 2009.
doi:10.1016/j.jaci.2008.10.059

Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria

To the Editor:

Kaplan et al¹ recently reported on the beneficial effect of omalizumab in 12 patients with chronic autoimmune urticaria. IgG autoantibodies to the α -subunit of the high-affinity IgE receptor cause the urticaria in many patients with this condition. Kaplan et al¹ propose that omalizumab may downregulate Fc ϵ RI expression, preventing mast cell activation by the IgG autoantibodies. Anti-CD20 mAb therapy, which abrogates the production of IgG autoantibodies, may be just as effective if not more effective

in this disease. I report here for the first time on the complete resolution of symptoms and discontinuation of rescue medication in a patient with severe chronic autoimmune urticaria who was treated with rituximab.

A 12-year-old boy with no significant family history presented with chronic urticaria and intermittent facial angioedema only partly responsive to regular oral desloratadine. He had developed insulin-dependent diabetes at 11 years and had a history of recurrent otitis media in early childhood and pneumonia at 6 years. Examination was normal, and there was no bronchiectasis on computed tomography scan. Serum immunoglobulins were low (IgM, 0.33 g/L [0.56-2.60]; IgG, 4.12 g/L [7.68-17.28]; IgA < 0.07 g/L; IgE < 2 kU/L). Although specific antibodies to tetanus and *Haemophilus influenzae* B were adequate, responses to measles, mumps, rubella vaccine and Pevnar (Wyeth Pharmaceuticals, Maidenhead, United Kingdom) were poor. A heterozygous P251L missense mutation was found in his transmembrane activator and CAML interactor (*TACI*) gene, but in neither parent.² He was started on regular immunoglobulin replacement therapy (0.4 g/kg/3 weeks), his urticaria improved, and he was able to discontinue the antihistamines. Two years later, he developed severe chronic urticaria and angioedema uncontrolled with regular antihistamines. Prednisolone at a dose of 20 to 30 mg per day controlled his symptoms but resulted in poor glycemic control and breakthrough symptoms when the dose was reduced. The patient was therefore given 4 intravenous infusions of rituximab (375 mg/m²) in October 2007. Within 1 week of the first dose, his urticaria and angioedema resolved completely, and he was able to discontinue all antihistamines and prednisolone. He remained totally asymptomatic for 12 months before urticaria controlled with desloratadine recurred.

As well as B-lymphoproliferative disease, B-cell-targeted therapies are increasingly being used for the treatment of a variety of immune disorders mediated by autoantibodies.^{3,4} In chronic autoimmune urticaria, targeting of B-lymphocytes producing IgG autoantibodies might be expected to be a more direct and thus effective therapy than neutralizing IgE with the hope of downregulating Fc ϵ RI expression. In this case, complete resolution of symptoms was noted within a week, compared with only 2 of 12 patients who responded within 4 weeks to omalizumab in the study by Kaplan et al.¹ There is only 1 previous published case that described rituximab having no beneficial effect in chronic urticaria.⁵ In this case, the history suggested a physical rather than autoimmune etiology, because the patient had no response to pulse methylprednisolone, azathioprine, or cyclosporine.

Further studies are required to determine the place not only of omalizumab but also of rituximab and other B-cell therapeutics in patients with severe chronic autoimmune urticaria. As an aside, it would also be interesting to investigate how many other patients with this condition harbor mutations in *TACI*.

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Disclosure of potential conflict of interest: The author has declared that he has no conflict of interest.

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doi:10.1016/j.jaci.2008.11.043

Reply

To the Editor:

Arkwright¹ presents an interesting case of chronic urticaria that was resistant to many therapeutic approaches, including corticosteroids and cyclosporine, but responded dramatically to rituximab. Because IgG₁ and IgG₃ contain the pathogenic autoantibodies in the autoimmune subgroup of patients with chronic urticaria,² the rationale for use of this agent is to target B-cell-producing IgG. The complete resolution of symptoms within 1 week of the first dose is not readily explicable by this mechanism because the half-life of IgG₃ (the IgG with the shortest half-life) is 7.5 to 9 days³; the half-life of IgG₁ is 18 to 23 days. Because the only other study of rituximab was negative,⁴ it is difficult to know whether the observation of Arkwright¹ represents a true response or a chance occurrence. In light of the unmet medical need in patients with chronic autoimmune urticaria, we agree that properly controlled studies of novel potential therapies should be considered.

The patient of Arkwright¹ is unusual because there is an associated immune deficiency characterized by hypogammaglobulinemia (including low IgE) and a mutation in the transmembrane activator and calcium moderator and cytophilin ligand interactor (*TACI*) gene. Although routine screening for *TACI* mutations in patients with chronic urticaria is not feasible, the coincidence of hypogammaglobulinemia and chronic urticaria is rare.

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Disclosure of potential conflict of interest: A. P. Kaplan receives honoraria from Sanofi-Aventis, is on the advisory board for Lev Pharmaceuticals and Sanofi-Aventis, and receives grant support from Lev Pharmaceuticals and Novartis Pharmaceuticals Corp. R. J. Maykut is employed by Novartis Pharmaceuticals Corp and has stock options and restricted stock in Novartis Pharmaceuticals Corp. The rest of the authors have declared that they have no conflict of interest.

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doi:10.1016/j.jaci.2008.11.044

Complementary and alternative medicine education: Need for expanded educational resources for American Academy of Allergy, Asthma & Immunology members

To the Editor:

When one searches the peer-reviewed medical literature using the terms *complementary medicine*, *alternative medicine*, *integrative medicine*, and *complementary and alternative medicine*, more than 5300 citations in the English language appear, with more than 90% dated after 1990 and more than 80% in the past decade alone. Meanwhile, the popular forum of the Internet, using the same combinations of terms, yields over 33 million hits in Google and more than 90 million in Yahoo search engines. The explosion of information in scientific journals dealing with complementary and alternative medicine (CAM) therapies has become overwhelming for allergists-immunologists and other traditional medical practitioners. In the face of increasing demands by patients and their advocates for support in the empiric trial of 1 or more CAM therapies, physicians are seeking balanced educational opportunities and trustworthy, as well as efficient, references addressing questions that arise in routine practice. The specialty of allergy-immunology is particularly challenged because conditions like allergic rhinitis, asthma, sinusitis, and immune deficiency are frequently cited as diseases that are responsive to nonallopathic medicines or practices.

The Complementary and Alternative Medicine Committee of the American Academy of Allergy, Asthma & Immunology (AAAAI) conducted a survey of the membership in the fall of 2007 to quantify the interest in development of expanded educational support and references related to objective reviews of CAM therapies. Between November 15 and December 15, 2007, a brief survey on membership interest in CAM therapies was distributed to more than 5000 members, with a total return of 420 surveys (approximately 8% return). In response to the lead question regarding interest in learning more about CAM, 80% (n = 337) responded yes, with 76% of respondents 40 years of age or older and the male/female ratio being 59%/40% (1% nonresponse).

Subsequent detailed questions were focused on understanding the scope of this interest and how it might affect AAAAI resource development in the future. The majority of respondents (87%) were physicians with more than 10 years in practice (69%). Only 3% of the responding membership had credentials or secondary licenses in CAM (mostly osteopathy). Only 6% have participated in prior CAM research, and 2% have published any articles on CAM,¹⁻³ but 39% indicated an interest in participating in further CAM research.

In response to the question about CAM therapeutic modalities of greatest interest to the respondents, more than 50% were interested in learning more about the following therapeutic modalities (ranked in order of interest from 88% to 27%, the top 10 from highest at 88% for herbal and botanical medicine through naturopathy at 51% are detailed in Table I). It is noteworthy that the interest to use CAM therapies for their patients mirrors the prioritization for interest in learning more and largely matches the top 10 modalities currently used (except for prayer at 11%). Definitions and descriptions of each of the therapeutic modalities are detailed on National Institutes of Health Web site.⁴

Of particular interest is the fact that when questioned about the use of CAM for themselves or their immediate families, the following uses were listed (n = 337): disease prevention (20.8%), disease treatment (18.1%), mental health (14.2%), relaxation