Allergen-specific IgG Antibodies for Cat Allergy?

Increased global prevalence of IgE-mediated allergies has led to increased morbidity. IgE-mediated allergies are caused by exposure to specific allergens in foods, pollen, mold, animals, insects, and others. Allergic diseases include allergic rhinitis, allergic asthma, atopic dermatitis, food allergy, and allergic rhinoconjunctivitis. Reactions can be mild to severe. In some cases, like in those with cat allergies, systemic reactions leading to status asthmaticus or anaphylaxis, potentially life-threatening conditions, can occur. Pharmacotherapy to prevent and treat symptoms typically includes antihistamines, β_2-agonists, topical corticosteroids, mast cell stabilizers, and leukotriene inhibitors. At the current time, allergen immunotherapy (AIT) is the only disease-modifying treatment that alters the course of immune response, with benefits often observed even after cessation of therapy (1), but now there could be a new approach on the horizon.

The work by Shamji and colleagues (pp. 23–33) in this issue of the *Journal* (2), and the 2018 study by Orengo and colleagues (3), report successful AIT for cat allergy and potentially, if verified by larger trials, could lead to a major leap forward for AIT. Allergens used for cat allergy AIT, both sublingual and subcutaneous, have progressed from crude extracts to sophisticated and targeted allergens. Crude cat allergen extracts were used for AIT through the mid-1990s (4); subsequent studies used extracts of Fel d 1 or recombinant Fel d 1, the major cat allergen (5). Overall, although some cat AIT studies with crude cat extracts or Fel d 1 have shown promising results in total rhinoconjunctivitis symptom scores, peak expiratory flow rate responses, medication scores, or allergen-specific or nonspecific bronchial provocation tests, others have found no significant differences between placebo and active groups (4). More recent studies have used an equimolar mixture of seven short synthetic peptides that corresponded to major T-cell epitopes, which were derived from the primary sequence of the major cat allergen Fel d 1 (Cat-PAD) (6). Although initial studies using Cat-PAD for cat allergy showed benefits, a larger 2016 phase 3 trial showed no difference between the placebo and active group in the mean combined score (combined total rhinoconjunctivitis symptom scores and rescue medication use score) (7). Safety data for cat AIT are limited because of the lack of high-quality placebo-controlled trials; however, reports of reactions requiring epinephrine have been reported (8). AIT may benefit those in whom allergies are not well controlled by pharmacotherapy or those who are monosensitized to Fel d 1.

The study by Shamji and colleagues in this issue of the *Journal* uses a novel approach to AIT. A common immunological response to AIT is an increase in allergen-specific IgG. Studies with aeroallergens and food allergens have indicated that desensitization with AIT is associated with increased IgG/IgE. The current hypothesis is that IgG competes with IgE for allergen binding, thereby decreasing IgE-mediated allergic response (9). To test this hypothesis, Orengo and colleagues developed two monoclonal IgG antibodies against Fel d 1 (REGN1908-1909) that bind simultaneously and noncompetitively to conformational epitopes of Fel d 1. They conducted a phase 1b, randomized, double-blind, placebo-controlled proof-of-mechanism study. Patients with cat allergy were administered a single subcutaneous dose of REGN1908-1909 ($n = 36$) or placebo ($n = 37$). Nasal allergen challenges were conducted at baseline and at Days 8, 29, 57, and 85 after treatment, and total nasal symptom scores were significantly reduced at all time points except Day 57. The study also found that REGN1908-1909 was well tolerated. A major benefit of the study was the rapid response from therapy, with benefits observed after a few days of prophylactic treatment rather than after many months of traditional AIT therapy.

Furthermore, the positive clinical data was supported by mechanistic data. Shamji and colleagues evaluated serum and nasal fluid from patients treated with REGN1908-1909 and found that it inhibited allergen-IgE complex binding to B cells. Compared with control subjects, patients treated with REGN1908-1909 also had a reduced number of cytokines associated with type 2 reactions (IL-4, IL-5, and IL-13) as well as inflammatory markers (CCL17/TARC and CCL5/RANTES). These study results lend support to the major role of the IgG/IgE ratio in desensitization with AIT.

This new approach to AIT could greatly add to the way we treat allergies. Typically, in AIT, the allergen is administered (generally orally, subcutaneously, or sublingually) with gradually increasing doses of the allergen over a period of time until the individual becomes desensitized (10). However, currently, whole foods or crude extracts of the allergen are often used, and there is great need for more U.S. Food and Drug Administration–approved AIT with regulation and standardization of the allergens. In the last few decades, great inroads in understanding the mechanisms underlying successful AIT have been made. Overall, there is a shift from a T-helper cell type 2 type allergenic response to a T-helper cell type 1 tolerogenic response, leading to increased production of allergen-specific IgE, which interacts with high-affinity FcεR1 receptors on the surface of mast cells and basophils, priming these cells toward an allergic response on subsequent allergen encounters (11). These mechanistic insights have further assisted with the development of safer and more effective AIT therapies. Examples include the use of anti-TSLP antibody, anti-IgE antibody, or anti IL-4Rα antibody in conjunction with AIT for allergy. Combining these monoclonal antibodies with AIT has been shown to significantly decrease the frequency and severity of reactions while decreasing the length of AIT from years to months (12). The use of monoclonal IgG antibodies (like those against Fel d 1 [REGN1908-1909]) offers additional breakthrough approaches to inhibit and hopefully treat allergies.

This is a promising area of research. Development of specific antiallergen IgG antibodies may potentially be a viable therapeutic

Originally Published in Press as DOI: 10.1164/rccm.202103-0662ED on April 15, 2021

Am J Respir Crit Care Med Vol 204, Iss 1, pp 1–13, Jul 1, 2021
Internet address: www.atsjournals.org

modality for the treatment of IgE-mediated allergies, including those to various foods, animal danders, insects, venoms, drugs, and aeroallergens. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Kari C. Nadeau, M.D., Ph.D.
Sean N. Parker Center for Allergy and Asthma Research
Stanford University
Stanford, California

ORCID ID: 0000-0002-2146-2955 (K.C.N.).

References

1. Nelson HS. The evolution of allergy immunotherapy. *Ann Allergy Asthma Immunol* 2021;126:357–366.
2. Shamji MH, Singh I, Layhadi JA, Ito C, Karamani A, Kouser L, *et al.* Passive prophylactic administration with a single dose of anti–Fel d 1 monoclonal antibodies REGN1908–1909 in cat allergen–induced allergic rhinitis: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* 2021;204:23–33.
3. Orengo JM, Radin AR, Kamat V, Badithe A, Ben LH, Bennett BL, *et al.* Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement. *Nat Commun* 2018;9:1421.
4. Dhami S, Agarwal A. Does evidence support the use of cat allergen immunotherapy? *Curr Opin Allergy Clin Immunol* 2018;18:350–355.
5. Grönlund H, Saarne T, Gafvelin G, van Hage M. The major cat allergen, Fel d 1, in diagnosis and therapy. *Int Arch Allergy Immunol* 2010;151:265–274.
6. Patel D, Couroux P, Hickey P, Salapatek AM, Laidler P, Larche M, *et al.* Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. J Allergy Clin Immunol 2013;131:103-109, e101–107.
7. Circassia Pharmaceuticals. Circassia announces top-line results from cat allergy phase III study. 2016 [accessed 2021 March 10]. Available from: https://www.circassia.com/media/press-releases/circassia-announces-top-line-results-from-cat-allergy-phase-iii-study/.
8. Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, Cuesta-Herranz C, Blanco-Quirós A. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. *J Allergy Clin Immunol* 1994;93:556–566.
9. Kanagaratham C, El Ansari YS, Lewis OL, Oettgen HC. IgE and IgG antibodies as regulators of mast cell and basophil functions in food allergy. *Front Immunol* 2020;11:603050.
10. Alvaro-Lozano M, Akdis CA, Akdis M, Alviani C, Angier E, Arasi S, *et al.* EAACI allergen immunotherapy user's guide. *Pediatr Allergy Immunol* 2020;31:1–101.
11. Celebi Sözener Z, Mungan D, Cevhertas L, Ogulur I, Akdis M, Akdis C. Tolerance mechanisms in allergen immunotherapy. *Curr Opin Allergy Clin Immunol* 2020;20:591–601.
12. Lin C, Lee IT, Sampath V, Dinakar C, DeKruyff RH, Schneider LC, *et al.* Combining anti-IgE with oral immunotherapy. *Pediatr Allergy Immunol* 2017;28:619–627.

Appraising the Real-Life Need for Extracorporeal Membrane Oxygenation during the COVID-19 Pandemic

The coronavirus disease (COVID-19) has become the leading cause of acute respiratory distress syndrome (ARDS) worldwide since January 2020. In a recent meta-analysis of 69 studies including 57,420 adult patients requiring invasive mechanical ventilation for COVID-19, the overall case fatality rate was estimated as 45% (95% confidence interval [CI], 39–52%) (1) and was higher than in the LUNG-SAFE cohort (40%; 95% CI, 38–42%) (2). Since the publication of the EOLIA trial (3) and its *post hoc* Bayesian analysis (4), venovenous extracorporeal membrane oxygenation (ECMO) has increasingly been used for patients with severe ARDS. As the COVID-19 pandemic drastically increased the demand for ECMO, data on the outcomes of this very specific population were eagerly awaited. In the largest series published to date, including 1,035 patients with COVID-19 from the Extracorporeal Life Support Organization registry, originating from 213 hospitals in 36 countries (5), the estimated 90-day probability of mortality was 37% (95% CI, 34–40%). It was 36% (95% CI, 27–48%) in a cohort of 83 ECMO-treated patients at the Paris-Sorbonne University hospitals in France (6). More recently, the 60-day mortality rate of 190 ECMO-treated patients with COVID-19–related ARDS in 55 centers in the United States was 33% (7). The authors performed an emulated target trial in this cohort, comparing patients initiated on ECMO in the first 7 days of ICU admission with those who did not receive ECMO, with lower mortality in the ECMO group (hazard ratio, 0.55; 95% CI, 0.41–0.74). These three cohorts reported early results with a significant proportion of patients without a final disposition at the end of follow-up. Moreover, these studies did not capture the overall proportion of mechanically ventilated patients with COVID-19 that required ECMO support at a regional or national level.

In this issue of the *Journal,* Diaz and colleagues (pp. 34–43) report the results of a population-based study focusing on patients with COVID-19–related ARDS treated with ECMO during the first wave of the pandemic in Chile (8). This is indeed the first cohort study evaluating the need for ECMO in COVID-19–related ARDS at a national level, in a country that has developed a coordinated national ECMO program (9, 10), using data from comprehensive national databases of mechanically ventilated and ECMO-treated patients. During the study period, 13 ECMO centers were commissioned by the Chilean National Advisory Commission to provide ECMO in adult patients with COVID-19.

Originally Published in Press as DOI: 10.1164/rccm.202104-0897ED on April 23, 2021