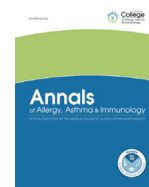




ELSEVIER

Contents lists available at ScienceDirect



Letter

rAsp f 3 and rAsp f 4 are associated with bronchiectasis in allergic fungal airways disease

Allergy to thermotolerant filamentous fungi, particularly *Aspergillus fumigatus*, is closely associated with fixed airflow obstruction, bronchiectasis, and other radiologically defined abnormalities, such as mucus plugging.¹ However, not all asthma patients who are immunoglobulin E (IgE) sensitized to *A fumigatus* develop these complications. To identify markers of poor outcomes in fungal allergy with asthma (and cystic fibrosis), the term allergic bronchopulmonary aspergillosis (ABPA) was coined. However, this syndrome was defined largely using criteria that represent a florid immunologic response to *A fumigatus* rather than clinically relevant outcomes, a problem that remains with the recent modifications recommended by the International Society for Human and Animal Mycology.² Moreover, asthma patients rarely fulfill all criteria for ABPA, whereas fungal allergy in asthma is common, particularly in more severe disease. Denning and colleagues proposed the term severe asthma with fungal sensitization (SAFS), essentially defined as ABPA with a low IgE, to define this larger group. However, not all asthma patients with fungal sensitization have severe disease and not all fungi are associated with lung damage.

In earlier work we proposed that, under the current state of knowledge, a more inclusive term, such as allergic fungal airways disease, should be used to describe asthma patients IgE sensitized to *A fumigatus* and related fungi.³ Irrespective of the terminology, there remains a need to identify biomarkers that distinguish between asthma patients with fungal IgE sensitization who will develop lung damage as a result of their asthma and those who will not develop such damage. In this study we aimed to determine whether specific IgE to different allergenic components of *A fumigatus* could be a more specific marker of lung damage in asthma compared with total specific IgE. Thus, the aim of our study was to determine the relationship between serum IgE to the allergen components Asp f 1–4 and Asp f 6 and fixed airflow obstruction, bronchiectasis, and other recognized radiologic markers of fungal allergy in a group of asthma patients with fungal sensitization. A secondary aim was to determine whether the components were useful in distinguishing between asthma patients who meet the criteria for ABPA, SAFS, or neither subset.

The majority of fungal extracts used to measure specific IgE use crude extracts that contain nonallergenic and allergenic proteins,

polysaccharides, and lipids that have been shown to cross-react both between and within species.⁴ Molecular-based allergy (MA) diagnostics benefit from being standardized, have a low degree of variability, and have been developed from either recombinant or purified native molecules.⁵ Studies investigating the ability of specific IgE components to *A fumigatus* to differentiate between ABPA and sensitization to *A fumigatus* have shown conflicting results. rAsp f 3, rAsp f 4, and rAsp f 6 have been demonstrated to be specific markers for ABPA in both cystic fibrosis and asthma,^{6,7} with Asp f 1 and f 2 also having been shown to be diagnostic markers of ABPA with area-under-the-curve values of 0.75 and 0.78, respectively, in a Japanese asthma population.⁸ However, as noted previously, the relevance of these observations to clinical outcomes remains unclear.

In this study we measured concentrations of IgE to the molecular allergens rAsp f 1–4 and rAsp f 6 in asthma patients recruited opportunistically from asthma and fungal allergy clinics by A.J.W. These patients represented a subset of participants recruited for a larger study.¹ Inclusion criteria were a positive specific IgE to *A fumigatus* (>0.35 kU/L) using the Phadia ImmunoCAP system, with a bias in recruitment toward those with a serum IgE of >1.0 IU/L. Demographics (age, sex, body mass index), clinical data (age of asthma diagnosis, asthma duration, Global Initiative for Asthma [GINA] status, and sputum cell counts), and spirometry data were collected during a stable visit using standard methods, recording post-bronchodilator forced expiratory volume in 1 second (percent predicted). High-resolution computed tomography scans were undertaken of the whole thorax using a spiral scanner (Siemens Somatom Definition AS Plus, Siemens Healthcare, Knoxville, Tennessee). Bronchiectasis (present/absent) was scored based on the radiologist's report. Descriptive statistics, analyzed using SPSS for Windows (IBM SPSS, Inc, Armonk, New York), were expressed as mean (SD or 95% confidence interval) or median (interquartile range). Nonparametric data were analyzed using Spearman's correlation and the Dunn-corrected Kruskal-Wallis test for multiple-group comparisons.

Eighty-five asthma patients were recruited, of whom 57.8% (n = 44) were male, 91.8% (n = 78) had a GINA score ≥3, and the majority had either early-onset atopic disease (50.6%, n = 43) or late-onset eosinophilic asthma (40%, n = 34). There were no statistically significant differences in components when separated by GINA score, endotype, or atopic status. A total of 37.6% (n = 32) met the criteria for ABPA² and 21.2% (n = 18) met the criteria for SAFS, whereas the majority (41.2%, n = 35) were sensitized to *A fumigatus* but did not fit either of these diagnostic classifications. The differences between the levels of IgE to components in these groups were statistically significant (Table 1).

rAsp f 6 was the only component to correlate well with total IgE (r = .798, P < .001). Although significant at P < .05, the other

Disclosures: A.J.W. has been an advisory board member for GSK, Pulmocide, KNOPP, and Astra Zeneca. No other author has anything to disclose.

Disclaimer: The views expressed are those of the author(s) and not necessarily those of the National Health Service, National Institute for Health Research, or the Department of Health.

Funding Sources: This work was supported by the National Institute for Health Research Leicester Respiratory Biomedical Research Unit.

Table 1Differences in Components Between Asthma Patients With ABPA, SAFS, and Those Sensitized to *Aspergillus fumigatus*

	ABPA (n = 32)	SAFS (n = 18)	Sensitized to <i>A fumigatus</i> (n = 35)	P value
rAsp f 1	3.58 (0.27–15.95)	0.14 (0.13–1.05)	0.54 (0.17–5.15)	.002
AUC	0.68	0.25	0.50	
rAsp f 2	2.32 (0.26–9.72)	0.13 (0.05–0.66)	0.34 (0.07–2.11)	.001
AUC	0.73	0.29	0.42	
rAsp f 3	7.04 (1.04–14.65)	0.33 (0.01–1.58)	1.06 (0.1–9.79)	.002
AUC	0.68	0.27	0.49	
rAsp f 4	1.33 (0.15–7.39)	0.02 (0.01–0.07)	0.12 (0.02–0.85)	<.001
AUC	0.74	0.24	0.44	
rAsp f 6	0.20 (0.02–2.12)	0.01 (0.01–0.01)	0.04 (0.01–0.12)	<.001
AUC	0.71	0.23	0.49	
Positive components (n)				
1 or 2	21.9%	38.9%	37.1%	
3 or 4	43.8%	27.8%	37.1%	
5	28.1%	0%	5.7%	
Total IgE	2,613 (1,535–5,000)	244 (219–534)	1,078 (646–2,561)	<.001
IgE <i>A fumigatus</i>	36.45 (17.2–74.2)	5.87 (2.88–9.24)	10.7 (3.36–25.2)	<.001

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AUC, area under the curve; IgE, immunoglobulin E; SAFS, severe asthma with fungal sensitization. Data expressed as median (interquartile range).

components were only weakly correlated with total IgE, *A fumigatus* IgE, peripheral blood eosinophil count, and asthma duration.

No correlations were seen between rAsp f 1–4 or rAsp f 6 and post-bronchodilator forced expiratory volume in 1 second. Bronchiectasis was associated with higher level of rAsp f 3 (4.4 [0.81–12.9] vs 0.34 [0.07–3.91], $P = .008$) and rAsp f 4 (0.47 [0.03–3.16] vs 0.09 [0.01–0.35], $P = .033$). No other statistical differences were seen between the components and the frequency of the radiologic abnormalities studied (tree-in-bud, bronchial wall thickening, mucoid impaction, collapse/consolidation, air trapping, fleeting shadows, and fibrosis) although receiver-operating characteristic curves did show an area-under-the-curve value of 0.71 for rAsp f 4 in predicting the development of fleeting shadows.

In asthma patients sensitized to crude extracts of *A fumigatus*, irrespective of their diagnostic label, rAsp f 3 and rAsp f 4 were found to be associated with development of bronchiectasis. Thus, a potential role for sensitization to the allergens rAsp f 3 and f 4 in causing bronchiectasis is worthy of further study. rAsp f 4 was found to be related to the development of fleeting shadows, and total IgE was most closely related to Asp f 6, which is commonly increased in atopic dermatitis. Patients who fulfilled the criteria for ABPA had a higher level of components than those with SAFS or neither label, but this was to be expected because ABPA is defined by a florid immunologic response to fungal extracts. In conclusion, rAsp f 3 and rAsp f 4 may be markers for the development of bronchiectasis in allergic fungal airway disease.

Kerry Woolnough, MD
Michelle Craner, DipHE

Catherine H. Pashley, PhD

Andrew J. Wardlaw, MD, PhD

Department of Infection, Immunity and Inflammation

Leicester Institute for Lung Health

University of Leicester

Glenfield Hospital

Leicester, UK

aw24@le.ac.uk

References

- [1] Woolnough KF, Richardson M, Newby C, et al. The relationship between biomarkers of fungal allergy and lung damage in asthma. *Clin Exp Allergy*. 2017; 47:48–56.
- [2] Woolnough K, Fairs A, Pashley CH, Wardlaw AJ. Allergic fungal airway disease: pathophysiologic and diagnostic considerations. *Curr Opin Pulm Med*. 2015;21: 39–47.
- [3] Cramer R, Garbani M, Rhyner C, Huitema C. Fungi: the neglected allergenic sources. *Allergy*. 2014;69:176–185.
- [4] Canonica GW, Ansotegui IJ, Pawankar R, et al. A WAO-ARIA-GA(2)LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J*. 2013; 6:17.
- [5] Casaulta C, Fluckiger S, Cramer R, Blaser K, Schoeni MH. Time course of antibody response to recombinant *Aspergillus fumigatus* antigens in cystic fibrosis with and without ABPA. *Pediatr Allergy Immunol*. 2005;16:217–225.
- [6] Kurup VP, Banerjee B, Hemmann S, Greenberger PA, Blaser K, Cramer R. Selected recombinant *Aspergillus fumigatus* allergens bind specifically to IgE in ABPA. *Clin Exp Allergy*. 2000;30:988–993.
- [7] Vitte J, Romain T, Carsin A, et al. *Aspergillus fumigatus* components distinguish IgE but not IgG4 profiles between fungal sensitization and allergic bronchopulmonary aspergillosis. *Allergy*. 2016;71:1640–1643.
- [8] Tanimoto H, Fukutomi Y, Yasueda H, et al. Molecular-based allergy diagnosis of allergic bronchopulmonary aspergillosis in *Aspergillus fumigatus*-sensitized Japanese patients. *Clin Exp Allergy*. 2015;45:1790–1800.