Control of Allergic Rhinitis and Asthma Test with 1-week recall

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REFERENCES

1. Remington BC, Baumert JL, Blom WM, Houben GF, Taylor SL, Kruizinga AG. Unintended allergens in precautionary labelled and unlabelled products pose significant risks to UK allergic consumers. *Allergy*. 2015;70:813-819.
2. Versluis A, Knulst AC, Kruizinga AG, et al. Frequency, severity and causes of unexpected allergic reactions to food: a systematic literature review. *Clin Exp Allergy*. 2015;45:347-367.
3. Blom WM, Michelsen-Huisman AD, van Os-Medendorp H, van Duijn G, de Zeeuw-Brouwer ML, Versluis A, Castenmiller JJM, Noteborn HPJM, Kruizinga AG, Knulst AC, Houben GF. Accidental food allergy reactions: products and undeclared ingredients. *J Allergy Clin Immunol*. 2018 Jun 14. pii: S0091-6749(18)30853-4. https://doi.org/10.1016/j.jaci.2018.04.041. [Epub ahead of print]
4. Anibarro B, Seoane FJ, Mugica MV. Involvement of hidden allergens in food allergic reactions. *J Investig Allergol Clin Immunol*. 2007;17:168-172.
5. Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of food allergy in France. *J Allergy Clin Immunol*. 2001;108:133-140.
6. Fleischer DM, Perry TT, Atkins D, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics*. 2012;130:e25-32.
7. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, et al. Inadvertent exposures in children with peanut allergy. *Pediatr Allergy Immunol*. 2012;23:133-139.
8. Padua I, Moreira A, Moreira P, Barros R. Food allergy: practical approach on education and accidental exposure prevention. *Eur Ann Allergy Clin Immunol*. 2016;48:174-181.
9. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69:1008-1025.
10. Le TM, van Hoffen E, Pasmans SG, Bruijnzeel-Koomen CA, Knulst AC. Suboptimal management of acute food-allergic reactions by patients, emergency departments and general practitioners. *Allergy*. 2009;64:1227-1228.
11. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:992-1007.
12. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol*. 2010;125(2 suppl 2):S116-S125.

SUPPORTING INFORMATION

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Control of Allergic Rhinitis and Asthma Test with 1-week recall: Validation of paper and electronic version

To the Editor,

Both asthma and allergic rhinitis (AR) are high prevalence diseases that frequently occur simultaneously.[1,2] The Allergic Rhinitis and its Impact on Asthma initiative (ARIA) recognizes the need for a concomitant evaluation and treatment of asthma and AR.[1,2] The Control of Allergic Rhinitis and Asthma Test (CARAT)[3-5] measures control of both asthma and AR with a 4-week recall period. In a time where the use of mobile devices has grown, a new modality to monitor patients is at our disposal. An electronic CARAT questionnaire allows clinicians to gain more insight into the period between visits and therefore could be a convenient and reliable alternative to the use of the current paper version of the CARAT. The main purpose of this study was to investigate the psychometric properties of the CARAT with 1-week recall period as paper version (CARATp1) and as electronic version (CARATe1).

This is a diagnostic study with repeated measurements in four consecutive weeks. The study population consisted of consecutive Dutch primary care asthma patients who were referred by their general practitioner to the asthma/COPD service.[6] Inclusion criteria were

TABLE 1 Baseline characteristics

Variable	Value	N
Age, mean (SD)	53.2 (14.3)	111
Gender, n (% male)	49 (42.6)	115
Height, mean (SD)	173 (9.8)	115
BMI, mean (SD)	27.7 (5.8)	112
Current/ex-smokers, n (%)	68 (58.6)	123
Pack years, MED (IQR)[a]	11 (4.7-20.0)	62
Allergic rhinitis	52 (51.0)	102
Medication use (total, n)		123
SABA, n (%)	30 (24.4)	
LABA, n (%)	63 (51.2)	
LAAC, n (%)	12 (9.8)	
ICS, n (%)	77 (62.6)	
NCS, n (%)	20 (16.3)	
Antihistaminic agent, n (%)	12 (9.8)	
Other medication, n (%)	11 (8.9)	
No medication, n (%)	29 (23.6)	
Lung function[b]		
FEV_1, mean (SD)[c]	93.7 (15.5)	110
FVC, mean (SD)[c]	105.4 (16.2)	110
FEV_1/FVC, mean (SD)	74.0 (8.6)	111
ARIA classification (total, n)		52
Intermitting—mild, n (%)	11 (21.2)	
Intermitting—moderate/severe, n (%)	1 (1.9)	
Persistent—mild, n (%)	25 (48.1)	
Persistent—moderate/severe, n (%)	15 (28.8)	
VAS		
Airway symptoms, MED (IQR)[a]	20 (10-50)	116
Upper airway symptoms, MED (IQR)[a]	20 (0-50)	115
Lower airway symptoms, MED (IQR)[a]	20 (3.125-50)	116
GINA classification (total, n)		95
Well-controlled, n (%)	23 (24.2)	
Partly controlled, n (%)	42 (44.2)	
Uncontrolled, n (%)	30 (31.6)	
ACQ classification (total, n)		111
Well-controlled, n (%)	60 (54.1)	
Partly controlled, n (%)	29 (26.1)	
Uncontrolled, n (%)	22 (19.8)	
CARATp1		
Total score, MED (IQR)[a]	24 (18-27)	105
AR domain score, MED (IQR)[a]	8 (6-11)	112
Asthma domain score, MED (IQR)[a]	15 (11.5-17)	109

ACQ, asthma control questionnaire; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma initiative; CARAT, Control of Allergic Rhinitis and Asthma Test; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IQR, interquartile range; LAAC, long-acting anticholinergic; LABA, long-acting beta-agonist; MED, median; NCS, nasal corticosteroid; p1, paper version with 1-wk recall period; SABA, short-acting beta-agonist; SD, standard deviation; VAS, Visual Analogue Scale.

[a]IQR of pooled data could not be calculated; [b]Postbronchodilation; [c]As percentage of predicted; nonimputed data were used for the descriptive statistics.

as follows: age 18-80 years and asthma diagnosis (made by a pulmonologist based on lung function tests including reversibility and self-reported questionnaires). Participation was voluntary, all patients received oral and written information about the study and all patients signed informed consent (study approved by the local medical ethics committee (METc 2014/578)).

In the period between January and August 2015, patients completed the following questionnaires on paper at baseline: CARATp1, ARIA[2] questions, Visual Analogue Scale (VAS)[7] on airway symptoms, ACQ[8] and GINA[9] questions. For 4 weeks (T1, T2, T3 and T4), the patients completed the CARATe1 each Monday and the CARATp1 every Tuesday. In the last week, the patients completed also the original CARAT on paper (CARATp4) and an evaluation form (see Table S1, Data S1). The CARAT contains ten questions concerning asthma symptoms (asthma domain) and AR symptoms (AR domain) in the previous 4 weeks and is administered on paper.[3-5] The only difference between the CARATp4 and the CARATp1 was the shorter recall period. The CARATe1 is an electronic application for smart devices developed by AstraZeneca. It shows, after a short instruction screen, the CARAT questions on ten consecutive screens.

The construct validity was calculated using Spearman correlation coefficient (ρ). The CARATp1 at baseline was compared with ARIA, VAS, GINA and ACQ (ρ 0.6-0.8 was expected).[10] The correlation between CARATp1 and CARATe1 was calculated using Spearman correlation coefficient ($\rho > 0.80$ was expected). The internal consistency of CARATp1 and CARATe1 was determined using Cronbach's alpha (α 0.70-0.95 was expected).[10] The test-retest reliability of CARATp1 and CARATe1 was evaluated with the intraclass correlation coefficient (ICC > 0.70 was expected).[10] Aforementioned analysis was performed with CARAT total scores, CARAT AR domain scores and CARAT asthma domain scores at T1, T2, T3 and T4. The average scores in each week of both CARATp1 and CARATe1 were calculated. Spearman correlations of both CARATp1 and CARATe1 with CARATp4 were calculated ($\rho > 0.80$ was expected). Statistical analysis was performed using SPSS 25 (IBM, Chicago, USA). Missing data were assumed to be missing at random and replaced using a multiple imputation procedure (see Data S1).

In this study, 123 patients were included for analyses and 23% of the AR patients reported intermitting AR (Table 1) (see Data S1). Construct validity of the CARATp1 was shown by correlation coefficients within the expected range (ρ 0.584-0.718) with VAS, ACQ, ARIA and GINA. As expected, the highest correlation coefficients were found (a) between AR domain of the CARAT and ARIA and VAS upper airway symptoms; and (b) between the asthma domain of the CARAT and GINA, ACQ and VAS lower airway symptoms (Table 2).

CARATp1 was highly correlated with CARATe1 (ρ 0.856-0.923). Internal consistency of both CARATp1 and CARATe1 was good (α 0.754-0.874) as was the test-retest reliability (ICC 0.722-0.931).

CARATp1 and CARATe1 correlated well with the CARATp4 (0.880 and 0.833, respectively). The correlation coefficients of the CARATp4 and the scores in each week of the CARATp1 were 0.680, 0.812, 0.857 and 0.895, respectively. The correlation coefficients of the CARATp4 and the scores in each week of the CARATe1 were 0.643, 0.720, 0.817 and 0.806, respectively.

The majority of patients (93%) considered the electronic version to be easy or very easy to complete and only 6% preferred the paper version (see Figure S1, Data S1).

This study found that the paper and electronic CARAT questionnaires with a 1-week recall period are valid and reliable, with comparable psychometric properties as the original CARAT4p.[3,4] CARATp1 and CARATe1 were strongly correlated with the original CARAT4p. Also, CARATp1 and CARATe1 were closely correlated. Moreover, the patients participating in this study considered the CARATe1 to be user-friendly. The clinical relevance of these findings is that both new versions of the CARAT are suitable questionnaires for clinical practice and clinical research in patients with asthma and AR in which the control of both diseases is the outcome of interest.

TABLE 2 Spearman correlation in absolute figures as estimation of construct validity of the CARATp1 at baseline

	VAS					
	Airway symptoms	Upper airway symptoms	Lower airway symptoms	GINA	ACQ	ARIA
CARATp1 (total)						
Correlation	**0.602**	0.481	0.580	0.555	0.647	0.612
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CARATp1 (AR)						
Correlation	0.347	**0.584**	0.241	0.166	0.309	**0.603**
P-value	<0.001	<0.001	0.007	0.108	0.001	<0.001
CARATp1 (Asthma)						
Correlation	0.645	0.257	**0.705**	**0.659**	**0.718**	0.373
P-value	<0.001	0.004	<0.001	<0.001	<0.001	0.006

All bold printed figures were expected to be >0.60.

ACQ, asthma control questionnaire; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma initiative; CARAT, Control of Allergic Rhinitis and Asthma Test; GINA, Global Initiative for Asthma; p1, paper version with 1-wk recall period; VAS, Visual Analogue Scale.

Interestingly, the correlation of the CARATp4 with the scores in individual weeks of the CARATp1 and the CARATe1 showed increasing correlation coefficients. In both cases, the correlation with the CARATp4 tends to rise as the questionnaires with 1-week recall are completed closer in time to when the CARATp4 was completed. This may suggest that recent weeks play a more prominent role in the assessment of the patient when completing the CARATp4 than the first weeks in the recall period. One may argue to prefer the CARAT with 1-week recall period to minimize recall bias.

The CARATe1 was viewed favourably by most patients in this study. Only 6% preferred the CARATp1. This may not be surprising considering the high level of integration in daily life of smart devices. However, one patient considered the CARATe1 to be very hard to complete (65-year-old woman). Although this is just one case, it shows that the paper version of the CARAT should not be fully discarded (see Data S1).

Future research should focus on the calculation of the CARAT's cut points to differentiate between controlled and uncontrolled asthma and AR. In addition, the effects of implementation of the CARATe1 on control and management in primary care should be investigated. This study showed that both new versions of the CARAT could be used as convenient tools for both patient and clinician to gain more insight into the control of asthma and AR.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests related to the submitted work. TvdM is currently an employee of GSK.

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AUTHOR CONTRIBUTIONS

TvdM, IT, JK and BF contributed to conception and design; HB, CdJ, EvH and JdK acquired the data; HB, CdJ, JF, BK and BF analysed and interpreted the data; HB, CdJ, JdK and BF drafted the article; JF, EvH, BK, TvdM, IT and JK revised it critically for important intellectual content; and all authors approved the final version to be published.

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REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R, Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA dissemination committee report. *Allergy*. 2004;59(5):469-478.
2. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the world health organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63 (suppl 86):8-160.
3. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. *Allergy*. 2010;65(8):1042-1048.
4. van der Leeuw S, van der Molen T, Dekhuijzen PN, et al. The minimal clinically important difference of the control of allergic rhinitis and asthma test (CARAT): cross-cultural validation and relation with pollen counts. *NPJ Prim Care Respir Med*. 2015;25:14107.
5. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, et al. Control of allergic rhinitis and asthma test (CARAT) can be used to assess individual patients over time. *Clin Transl Allergy*. 2012;2(1):16.
6. Metting EI, Riemersma RA, Kocks JH, Piersma-Wichers MG, Sanderman R, van der Molen T. Feasibility and effectiveness of an asthma/COPD service for primary care: a cross-sectional baseline description and longitudinal results. *NPJ Prim Care Respir Med*. 2015;25:14101.
7. Bousquet PJ, Combescure C, Klossek JM, Daures JP, Bousquet J. Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis. *J Allergy Clin Immunol*. 2009;123(6):1349-1354.
8. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907.

9. FitzGerald J, Bateman E, Boulet L, et al. Global strategy for asthma management and prevention pocketguide. http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2016. Accessed 28 July, 2016.
10. Terwee CB, Bot SD, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol*. 2007;60(1):34-42.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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De novo sensitization to *Aspergillus fumigatus* in adult asthma over a 10-year observation period

To the Editor,

Although exposure and sensitization to respiratory allergens are key in asthma presentation,[1] few studies have investigated longitudinal changes in sensitization profiles to respiratory allergens among individuals with asthma.[2] Recently, exposure and sensitization to fungal allergens as risk factors for more persistent, severe asthma have been investigated.[3–6] Considering the chronicity of asthma pathogenesis, changes in sensitization profiles to respiratory allergens can occur temporally and influence prognosis. Physicians sometimes encounter de novo sensitization (DNS) to *Aspergillus fumigatus* (Af), accompanied by allergic bronchopulmonary aspergillosis (ABPA) onset among patients receiving long-term asthma treatment.[7] Despite its long-term impact on asthma management, risk factors for DNS to Af in asthma patients are unclear. We investigated longitudinal changes in sensitization profiles to respiratory allergens and factors associated with DNS to Af in asthma patients.

Asthma patients treated for ≥10 years at the Sagamihara National Hospital, a large tertiary-care hospital for allergic diseases in central Japan, were assessed. Levels of IgE antibodies (Abs) to allergen extracts from five common fungal allergens and to panels of respiratory allergen components were measured in sera obtained ≥10 years ago (1991-2004, **baseline**) and compared with those in recently sampled sera (2015, **follow-up**). Clinical features were compared between asthma patients with or without DNS to Af. Detailed study design (Figure S1) and methods are shown in the supporting information. The ethics committee of Sagamihara National Hospital approved the study protocol (No. 2016-023), and written informed consent was obtained.

To assess longitudinal changes in sensitization to respiratory allergens, data and sera from 139 subjects were analyzed (Study 1). IgE levels and rates of IgE positivity to respiratory allergens were compared between baseline and follow-up. Serum IgE and IgG levels to Af extract and serum IgE levels to allergen extracts of *Candida albicans*, *Trichophyton rubrum*, *Malassezia* spp., and *Alternaria alternata* were determined using a commercial ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden); IgE levels ≥0.35 kU_A/L were considered positive. Serum levels of IgE specific for native Der f 1 from house dust mites; nCry j 1, Japanese cedar; recombinant Phl p 1 and p 5, timothy-grass; rBet v 1, birch; nAmb a 1, ragweed; nArt v 1, mugwort; rCan f 1, dogs; rFel d 1, cats; rAlt a 1, *Alternaria alternata*; rAsp f 1, f 3, and f 6, Af; rCla h 8, *Cladosporium herbarum*; and rBla g 1, cockroaches were determined using a commercial ImmunoCAP Solid-Phase Allergen Chip (ISAC). IgE levels ≥0.3 ISAC standardized units (ISU) were considered positive.

Study 2 involved risk factor analysis for DNS to Af allergen. Nine organic lung disease patients at baseline and/or follow-up were excluded owing to their high susceptibility to *Aspergillus* infection (and accompanying IgE sensitization to Af). After excluding 12 additional patients positive for IgE to Af extract and/or rAsp f 1 at baseline, clinical characteristics of 118 patients were compared between those with or without DNS to rAsp f 1.

Table S1 presents the clinical characteristics of the patients at baseline and follow-up (Study 1). The median interval of serum sampling between baseline and follow-up was 19.1 (IQR, 14.9-21.4) years. Figure 1 and Tables S2 and S3 show the frequencies of positivity for and levels of IgE to each respiratory allergen. Frequencies of patients positive for IgE to Af extract and to rAsp f 1 noticeably increased (from 8.6% to 31% and from 0.7% to 13%, respectively) from baseline to follow-up. Table 1 shows the association between clinical parameters and DNS to rAsp f 1 after adjusting with serum sampling interval (Study 2). Among 118 patients, 14 displayed DNS to rAsp f 1. Male sex, decreased pulmonary function (FEV_1/FVC ratio <65%), nonatopic status at baseline, elevated total IgE levels (>417 IU/mL), and medium-to-high dose of ICS (≥500 μg/day) at follow-up were associated with DNS to rAsp f 1. Among these 14 patients with DNS to rAsp f 1, two and six patients satisfied the diagnostic criteria for ABPA and SAFS, respectively (data not shown).

To our knowledge, this is the first study to clearly document longitudinal changes in respiratory allergen sensitization and identify factors associated with DNS to Af. Notably, IgE positivity frequencies against Af extract and rAsp f 1 increased considerably. Our findings from component-based IgE measurements indicate genuine changes in sensitization profiles to panels of respiratory allergens.[8]