PROF. OLIVER PFAAR (Orcid ID : 0000-0003-4374-9639)

PROF. GIORGIO WALTER CANONICA (Orcid ID : 0000-0001-8467-2557)

PROF. LUDGER KLIMEK (Orcid ID : 0000-0002-2455-0192)

PROF. TORSTEN ZUBERBIER (Orcid ID : 0000-0002-1466-8875)

PROF. JEAN BOUSQUET (Orcid ID : 0000-0002-4061-4766)

Article type : Letter to the Editor

Effects of allergen immunotherapy in the MASK-air study: a proof-of-concept analysis

Manuscript Acceptance Date: 19-May-2021

To the Editor,

Allergen immunotherapy (AIT) is effective in allergic rhinitis (AR) and/or asthma. Randomized controlled trials (RCTs) have demonstrated efficacy and safety of both subcutaneous (SCIT) and sublingual (SLIT) in patients allergic to pollen and house dust mites. [1] RCTs are mandatory for market authorization of AIT products but they lack real-world data (RWD). Many AIT guidelines have been formulated but they have not imputed RWD.

Observational studies with RWD complement RCTs and provide novel information on AIT in real life. The European Academy of Allergy and Clinical Immunology (EAACI) emphasized the value of RWD data in AIT [2].

This proof-of-concept (POC) study aimed to assess the effects of AIT in AR using RWD obtained with a validated app (MASK-air®), a Good Practice of DG Santé.[3,4]

Methods

All MASK-air® data from May 21, 2015 to December 6, 2020, in 25 countries have been analysed. MASK-air® comprises a daily questionnaire in which users are asked to answer six questions assessing AR symptoms visual analogue scales (VASs), and provide information on AIT and medication.

Days of participants using AIT use were compared to days from non-AIT participants using (i) daily global symptoms VAS (how much allergy symptoms were bothering the user), and ii) work VAS (impact of allergic symptoms on work). Separate analyses were performed for (i) days when no medication, (ii) days with monotherapy (single drug formulation), and (iii) days with co-medication (more than one drug formulation) were used. Sensitivity analyses were performed with the AIT group comprising data from users under AIT irrespective of the days when AIT was effectively done.

Continuous variables are presented as medians (with 95% confidence intervals [CI]) and interquartile ranges (IQR). Median VAS values were compared using the Mann-Whitney U test.

Results

317,176 days of MASK-air® (17,870 users) were analysed, of which 138,304 (43.6%) involved the reporting of medication(s) and 36,229 (11.4%) of AIT.

We observed a global symptoms median VAS of 9 (95%CI=[9-9]) for days of users treated by AIT *versus* 12 (95%CI=[12-12], p<0.001) for days of non-AIT users (Table 1). The median global symptoms VASs were lower even when considering (i) days under no medication (7 *versus* 8), (ii) days under monotherapy (11 *versus* 14), or (iii) days under co-medication (17 *versus* 20).

Similar results were found i) for Work VAS (Table 1) and ii) for data of users reporting the use of AIT (Supplementary Table 1).

Table 1: Impact of AIT on real world data using MASK-air®

Medication scheme	***N* observations (%)**		**Symptoms VAS – median [95%CI] (IQR)**		**P value**
	AIT	**No AIT**	**AIT**	**No AIT**	
All observations	36,229 (11.4)	280,947 (88.6)	9 [9-9] (24)	12 [12-12] (28)	<0.001

All observations	36,229 (11.4)	280,947 (88.6)	9 [9-9] (24)	12 [12-12] (28)	<0.001
No medication	21,613 (12.1)	157,259 (87.9)	7 [6-7] (19)	8 [8-8] (24)	<0.001
Single medication	8712 (10.4)	75,291 (89.6)	11 [11-12] (24)	14 [14-15] (28)	<0.001
Comedication	5904 (10.9)	48,397 (88.1)	17 [16-18] (31)	20 [19-20] (35)	<0.001

Medication scheme	***N* observations (%)**		**Work VAS – median [95%CI] (IQR)**		
	AIT	**No AIT**	**AIT**	**No AIT**	
All observations	17,730 (11.8)	132,002 (88.2)	6 [6-6] (18)	8 [8-8] (23)	<0.001
No medication	10,465 (12.5)	73,024 (87.5)	4 [4-4] (15)	5 [5-6] (18)	<0.001
Single medication	4472 (11.0)	35,997 (89.0)	8 [7-8] (18)	10 [10-10] (23)	<0.001
Comedication	2793 (10.8)	22,981 (88.2)	12 [11-13] (27)	15 [14-15] (30)	<0.001

CI=Confidence interval; IQR=Interquartile range; Symptoms VAS = MASK-air® visual analogue scale assessing the severity of overall allergic symptoms on that day; Work VAS = MASK-air® visual analogue scale assessing the work impact of allergic symptoms on that day

Conclusions and limitations

This POC indicates that MASK-air® is a valuable tool for assessing AIT. The results of this study accord with previous studies in 3,000 and 9,900 patients.[5] The overall effect on VAS global symptoms or work is around 25%. Interestingly, the same magnitude of effect is observed for days without treatment, monotherapy and co-medication.

Median levels of VAS are low, and this can be explained by variable exposure to allergens, patients continuing their treatment without allergen exposure, and effective treatment (Table 2, from data previously published [6]).

Table 2: Differences in VAS global symptoms during and outside of the expected pollen season in the European dataset of MASK [6]

	FF	**MPAzeFlu**	**MF**	**OAH mono**	**No treatment**

During pollen season					
N observations/days (*N* users)	3286 (331)	2594 (159)	4093 (351)	9780 (1414)	23377 (3736)
VAS day 1 – median [p25-p75]	50 [28-71]	52 [25-73]	50 [30-75]	55 [30-75]	40 [15-56]
VAS all days – median [p25-p75]	26 [8-50]	16 [6-38]	19 [7-39]	14 [3-38]	14 [3-38]
Outside pollen season					
N observations/days (*N* users)	1116 (99)	1258 (80)	1437 (95)	1956 (275)	13,120 (1299)
VAS day 1 – median [p25-p75]	44 [19-67]	34.5 [15-62]	46 [17-64]	38 [18-66]	29 [6-50]
VAS all days – median [p25-p75]	19 [5-44]	18 [7-36]	14 [5-34]	19 [5-47]	5 [0-20]

These results show: (i) symptoms on day 1 are more severe than during the course of the study. This suggests that treatment is effective and/or that exposure to allergen varies; (ii) symptoms on day 1 are more severe during the pollen season than outside; and (iii) median symptoms on day 1 during the pollen season are moderate for OAH mono and moderate-severe for INCS. FF=Fluticasone Furoate; MF=Mometasone Furoate; MPAzeFlu=Azelastine-Fluticasone-Propionate; OAH=Oral antihistamines; VAS=Visual analogue scale (assessing the severity of overall allergic symptoms on that day); p25-p75=percentile 25-percentile 75.

Patients used the app for an average of 17.5 days. Since data of the allergen exposure (particularly on the daily amounts of pollen for each region) are not available yet, it was not possible to refer to patients' personalized pollen exposure or to exclude days without allergen exposure from this analysis. Another limitation concerns the possibility of differences in care and adherence between users who regularly receive AIT or not. However, this study was not designed to compare the magnitude of efficacy of different AIT products, to differentiate between administration routes or treatment schedules of AIT, or between allergens. It attempted to confirm the value of MASK-air® in AIT. Based on this POC-trial, subsequent analyses will investigate effect sizes of different routes of administration, allergen-groups, impact of natural allergen exposure, and country specific differences. [1]

References

1. Bousquet J, Pfaar O, Togias A, et al. 2019 ARIA Care pathways for allergen immunotherapy. *Allergy.* 2019;74(11):2087-2102

2. Paoletti G, DiBona D, Chu DK, et al. Allergen immunotherapy: the growing role of observational and randomised trial "Real-World Evidence". *Allergy.* 2021.

3. Bousquet J, Bedbrook A, Czarlewski W, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. *Clin Transl Allergy.* 2019;9:16.

4. Bousquet J, Anto JM, Bachert C, et al. ARIA digital anamorphosis: Digital transformation of health and care in airway diseases from research to practice. *Allergy.* 2021;76(1):168-190.

5. Bedard A, Basagana X, Anto JM, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. *J Allergy Clin Immunol.* 2019;144(1):135-143 e136.

6. Bedard A, Basagana X, Anto JM, et al. Treatment of allergic rhinitis during and outside the pollen season using mobile technology. A MASK study. *Clin Transl Allergy.* 2020;10(1):62.

Oliver Pfaar, Department of Otorhinolaryngology, Head and Neck Surgery,
Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg , Germany. ORCID: 0000-0003-4374-9639

Bernardo Sousa-Pinto, MEDCIDS – Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal; Center for Health Technology and Services Research (CINTESIS), Porto, Portugal. ORCID: 0000-0002-1277-3401

Philippe Devillier, Laboratory of Research in Respiratory Pharmacology, VIM Suresnes, UMR-0892, Université Paris Saclay and Department of Airway Diseases, Hôpital Foch, Suresnes, France. ORCID: 0000-0001-6054-1886.

G. Walter Canonica, Personalized Medicine Asthma & Allergy Clinic-Humanitas University & Research Hospital-IRCCS-Milano Italy. ORCID: 0000-0001-8467-2557

Ludger Klimek, Center for Rhinology and Allergology, Wiesbaden, Germany. ORCID: 0000-0002-2455-0192

Torsten Zuberbier, Department of Dermatology, Venerology and Allergology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany. ORCID: 0000-0002-1466-8875

João Fonseca, MEDCIDS – Department of Community Medicine, Information and HealthDecision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal; Patient-centred Innovation and Technologies group (PaCeIT), Center for Health Technology and Services Research (CINTESIS); Imunoalergologia, CUF, Porto, Portugal. ORCID - 0000-0002-0887-8796

Jean Bousquet, Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin, Germany, and CHU Montpellier and MACVIA, Montpellier, France. ORCID: 0000-0002-4061-4766

Corresponding author:

Oliver Pfaar

Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

Baldingerstraße,

D-35043 Marburg, Germany.

e-mail: oliver@pfaar.org

Conflict of Interest:

Dr. Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Indoor Biotechnologies, grants and personal fees from GlaxoSmithKline, personal fees from Astellas Pharma Global, personal fees from EUFOREA, personal fees from ROXALL Medizin, personal fees from Novartis, personal fees from Sanofi-Aventis and Sanofi-Genzyme, personal fees from Med Update Europe GmbH, personal fees from streamedup! GmbH, grants from Pohl-Boskamp, grants from Inmunotek S.L., personal fees from John Wiley and Sons, AS, personal fees from Paul-Martini-Stiftung (PMS), personal fees from Ingress-Health HWM, personal fees from Regeneron Pharmaceuticals Inc., outside the submitted work.

Dr. Devillier reports personal fees from ALK Abello, personal fees from Stallergenes Greer, outside the submitted work.

Dr. Klimek reports grants and personal fees from Allergopharma, grants and personal fees from MEDA/Mylan, personal fees from HAL Allergie, personal fees from ALK Abelló, grants and personal fees from LETI Pharma, grants and personal fees from Stallergenes, grants from Quintiles, grants and personal fees from Sanofi, grants from ASIT biotech, grants from Lofarma, personal fees from Allergy Therapeut., grants from AstraZeneca, grants and personal fees from GSK, grants from Inmunotek, personal fees from Cassella med, personal fees from Novartis, outside the submitted work; and Membership: AeDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV , GPA, EAACI.

Dr. Zuberbier reports personal fees from AstraZeneca, personal fees from AbbVie, personal fees from

ALK, personal fees from Almirall, personal fees from Astellas, personal fees from Bayer Health Care, personal fees from Bencard, personal fees from Berlin Chemie, personal fees from FAES, personal fees from HAL, personal fees from Leti, personal fees from Meda, personal fees from Menarini, personal fees from Merck, personal fees from MSD, grants and personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Stallergenes, personal fees from Takeda, personal fees from Teva, personal fees from UCB, grants from Henkel, personal fees from Kryolan, personal fees from L´Oréal, outside the submitted work; and Organizational affiliations: Commitee member: WHO-Initiative "Allergic Rhinitis and Its Impact on Asthma" (ARIA); Member of the Board: German Society for Allergy and Clinical Immunology (DGAKI); Board Chairman: European Centre for Allergy Research Foundation (ECARF) President: Global Allergy and Asthma European Network (GA2LEN); Member: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO).

The rest of authors have nothing to declare.