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

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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

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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

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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

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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]

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Conflict of Interest:

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The rest of authors have nothing to declare.

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Supplementary Table 1. Comparison of symptoms VAS (how much allergy symptoms were bothering the user), and Work VAS (impact of allergic symptoms on work) in observations of users treated with allergen immunotherapy (AIT) versus of users not treated with AIT the same day.

Medication scheme	*N* observations (%) [*N* users]		Symptoms VAS – median [95%CI] (IQR)		*P*-value
	AIT	No AIT	AIT	No AIT	
All observations	95,606 (31.2) [2197]	211,027 (68.8) [15,020]	8 [8-8] (22)	13 [13-13] (30)	<0.001
No medication	58,269 (34.0) [1773]	113,141 (66.0) [11,162]	6 [6-6] (17)	9 [9-9] (27)	<0.001
Single medication	22,142 (26.9) [1208]	60,090 (73.1) [6768]	12 [11-12] (24)	15 [15-15] (30)	<0.001
Comedication	15,195 (28.7) [787]	37,796 (71.3) [3810]	15 [15-16] (27)	21 [21-22] (37)	<0.001
Medication scheme	***N* observations (%) [*N* users]**		**Work VAS – median [95%CI] (IQR)**		***P*-value**
	AIT	**No AIT**	**AIT**	**No AIT**	
All observations	45,176 (31.2) [1663]	99,800 (68.8) [9910]	6 [6-6] (17)	9 [9-9] (25)	<0.001
No medication	27,740 (34.6) [1310]	52,383 (65.4) [7112]	4 [3-4] (13)	6 [6-6] (20)	<0.001
Single medication	10,760 (27.1) [865]	28,897 (72.9) [4345]	8 [7-8] (19)	11 [11-11] (24)	<0.001
Comedication	6676 [566]	18,520 [2480]	13 [12-13] (27)	15 [15-16] (31)	<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