Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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ORIGINAL ARTICLE

Rhinitis, Sinusitis and Upper Airway Disease

Comparison of rhinitis treatments using MASK-air® data and considering the minimal important difference

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Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; Aze-Flu, azelastine-fluticasone intranasal formulation; GDPR, general data protection regulation; GRADE, grading of recommendations, assessment, development and evaluation; INAH, intranasal H_1-antihistamine; INCS, intranasal corticosteroid; mHealth, mobile health; MID, minimal important difference; OAH, oral H_1-antihistamine; OCS, oral corticosteroid; OR, odds ratio; RCT, randomized clinical trial; VAS, visual analogue scale.

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Abstract

Background: Different treatments exist for allergic rhinitis (AR), including pharmacotherapy and allergen immunotherapy (AIT), but they have not been compared using direct patient data (i.e., "real-world data"). We aimed to compare AR pharmacological treatments on (i) daily symptoms, (ii) frequency of use in co-medication, (iii) visual analogue scales (VASs) on allergy symptom control considering the minimal important difference (MID) and (iv) the effect of AIT.

Methods: We assessed the MASK-air® app data (May 2015–December 2020) by users self-reporting AR (16–90 years). We compared eight AR medication schemes on reported VAS of allergy symptoms, clustering data by the patient and controlling for confounding factors. We compared (i) allergy symptoms between patients with and without AIT and (ii) different drug classes used in co-medication.

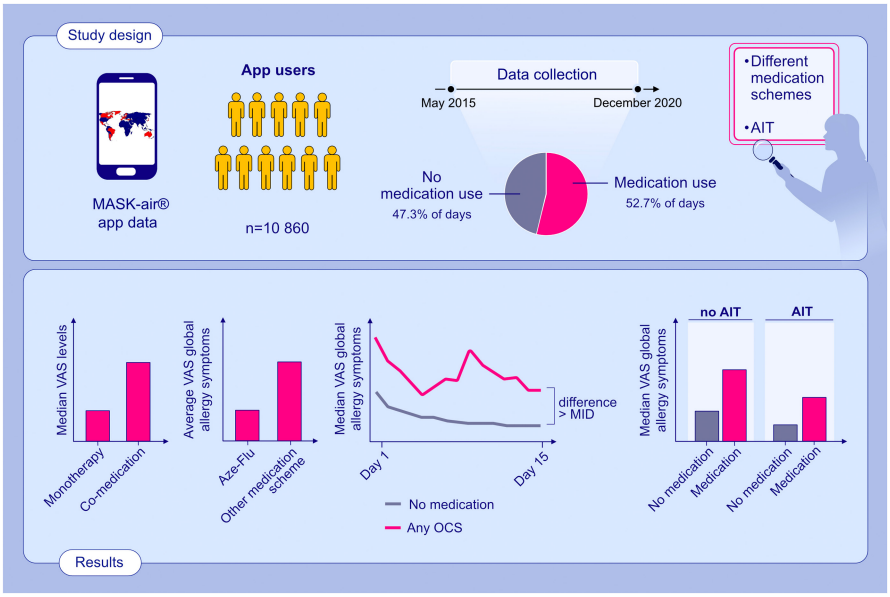
Results: We analysed 269,837 days from 10,860 users. Most days (52.7%) involved medication use. Median VAS levels were significantly higher in co-medication than in monotherapy (including the fixed combination azelastine-fluticasone) schemes. In adjusted models, azelastine-fluticasone was associated with lower average VAS global allergy symptoms than all other medication schemes, while the contrary was observed for oral corticosteroids. AIT was associated with a decrease in allergy symptoms in some medication schemes. A difference larger than the MID compared to no treatment was observed for oral steroids. Azelastine-fluticasone was the drug class

with the lowest chance of being used in co-medication (adjusted OR = 0.75; 95% CI = 0.71–0.80).

Conclusion: Median VAS levels were higher in co-medication than in monotherapy. Patients with more severe symptoms report a higher treatment, which is currently not reflected in guidelines.

KEYWORDS

allergen immunotherapy, allergic rhinitis, co-medication, multivariable mixed-effects model, real-world data



GRAPHICAL ABSTRACT

Median VAS levels for allergy symptoms are significantly higher in co-medication than in monotherapy schemes. Aze-Flu is associated with lower average VAS allergy symptoms and with lower chances of being used in co-medication than all other medication schemes. A difference larger than MID is observed for the comparison between oral steroids vs. no medication. AIT is associated with a decrease in VAS allergy symptoms on days with no medication or with medication.

Abbreviations: AIT, allegen immunotherapy; Aze-Flu, Azelastine-Fluticasone; INCS, intranasal corticosteroids; INHS, intranasal antihistamines; MID, minimal important difference; OAH, oral antihistamines; OCS, oral corticosteroids; VAS, visual analogue scale

1 | INTRODUCTION

In allergic rhinitis (AR) patients, the most frequently used medications include oral H_1-antihistamines (OAHs), intranasal H_1-antihistamines (INAHs), ocular H_1-antihistamines, intranasal corticosteroids (INCSs) and azelastine-fluticasone (Aze-Flu; a fixed intranasal formulation of an INAH and an INCS).[1] Some studies have attempted to rank AR medications based on their efficacy,[2] but data that mitigate concerns about indirectness that are common to randomized clinical trials (RCTs) are required. Mobile health (mHealth) apps such as MASK-air® can collect large volumes of direct patient data (often known as "real-world data"), offering new insights into AR management.[3–6] Three MASK-air® direct patient data cross-sectional studies have provided novel information on medication use and disease control in the everyday life of AR patients.[4,5] These studies found that AR control (assessed using visual analogue scales (VASs)) was similar for days under no treatment and for days under monotherapy with INCS or Aze-Flu. On the other hand, monotherapy with OAHs and the use of multiple treatments (co-medication) were associated with worse disease control. However, these studies did not cluster observations by patients and adjust for relevant potential confounders. In addition, the minimal important difference (MID) for VAS was not considered.

Addressing these gaps would strengthen the incorporation of results of large-scale direct patient data observational studies alongside RCTs and additive studies (e.g., allergen chamber studies assessing the speed of onset of medications[7,8]) into guidelines so that the revised next-generation Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines will use direct patient data instead of a consensus.[9]

This study aimed to assess medication schemes for monotherapy, co-medication and/or allergen immunotherapy (AIT) comparing (by means of multivariate mixed-effects models) whether VASs were

different across medication schemes, in particular considering the MID for VAS global allergy symptoms. We hypothesized that co-medication schemes or oral corticosteroid (OCS) use could be associated with a higher VAS than the remaining medication schemes (possibly with these differences in VASs being higher than the MID for VAS. This may enable physicians to be informed for their daily practice, and guideline developers to propose novel ARIA guidelines for AR treatment using a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach including direct patient data.

2 | METHODS

2.1 | Design of the study

We performed a cross-sectional observational study of the different medication schemes reported in MASK-air®. We compared different medication classes on VAS levels and their frequency of use in co-medication, applying models clustered at the patient level and adjusted for comorbidities, baseline severity and symptoms, the month of the year and use of AIT. Following a predefined plan, the main endpoint analyzed differences between treatments in VAS global allergy symptoms. Such differences were assessed considering the MID on that VAS. Secondary outcomes included (i) the comparison of VAS global allergy symptoms from patients under AIT or not, (ii) the comparison of VASs assessing individual AR symptoms (rhinitis, conjunctivitis) and the impact of AR on work and (iii) the comparison of the frequency of drug classes used in co-medication. All analyses were performed using the full MASK-air® dataset. Sensitivity analyses were performed during the first 2 weeks of reporting.

2.2 | Setting and participants

MASK-air® has been freely available since 2015 and is used in 28 countries (www.mask-air.com) via the Apple App and Google Play Stores.[6] In this study, we included the daily monitoring data from 25 different countries in users aged 16–90 years with self-reported AR from May 21, 2015 to December 6, 2020 according to methods previously described.[3,10] There were no exclusion criteria.

2.3 | Ethics

MASK-air® has a CE1 marking. It follows the General Data Protection Regulation (GDPR).[11] All data are anonymized (including data related to geolocation) using k-anonymity.[12] The database has been approved by the *Commission Nationale de l'Informatique et des Libertés*. An independent Review Board approval was not required since the study is observational, and all users agree in the terms of use to having their data analyzed.

2.4 | Data sources and variables

2.4.1 | MASK-air®

MASK-air® includes a daily monitoring questionnaire, with five mandatory questions assessing the impact of AR by means of VASs scaled from 0 to 100 (Table S1). In addition, users are asked to input their daily medications using a regularly-updated scroll list that contains all country-specific prescribed and over-the-counter medications (the International Nonproprietary Names classification is used for drug nomenclature[13]). This allows for the medications to be clustered in groups (e.g., OAH and INCS).

2.4.2 | Selection of medications

For the assessment and comparison of VASs, we considered eight medication schemes based on ARIA and US Practice Parameters (for monotherapy) and on a mixed hypothesis- and data-driven classification (for co-medication, as there is no classification for co-medication): (i) sole use of OAH or INAH, (ii) sole use of INCS, (iii) sole use of Aze-Flu, (iv) use of INCS + OAH, (v) use of Aze-Flu + other medications, (vi) use of INCS + OAH + other medications, (vii) use of OCS and (viii) any other AR medication/scheme. In addition, we compared (i) OAH, (ii) INAH, (iii) INCS, (iv) Aze-Flu, (v) OCS and (vi) other rhinitis drugs on their use in co-medication.

To follow the patients' perspectives more closely, monotherapy was defined as days when only one single drug formulation for AR was reported, even with more than one active compound[3,4,5] (e.g., nasal Aze-Flu contains two drugs but, as it is a fixed combination, it was considered as monotherapy). Co-medication was defined as days with two or more medications/drug formulations for AR. Asthma medications were not considered in co-medication.

2.5 | Size of the study

In this study, data from all registered users were included. No sample size calculation was performed.

2.6 | Biases

There are potential information biases related to the self-reported nature of data collection. Potential selection biases might be introduced because app users are not representative of all patients with AR (e.g., possible overrepresentation of users suffering from moderate-to-severe AR,[5] or overrepresentation of patients with clinically diagnosed AR using prescribed medications rather than over-the-counter medications). It is not known whether users fill in the MASK-air® daily monitoring questionnaire before or after treatment for a given day. Due to the size of each sample, we did not differentiate between sublingual and subcutaneous AIT. Finally, we included data from 2020, with the COVID-19 pandemic possibly having affected patient behaviour.

TABLE 1 Visual analogue scale (VAS) on global allergy symptoms by medication scheme

	N days (%)						Median VAS (P25-P75)	Average difference in VAS[a] (95% CI)
	Total	VAS = 0	VAS 1–19	VAS 20–49	VAS 50–74	VAS ≥ 75		
No treatment	127,565	38,680 (30.3)	55,837 (43.8)	23,117 (18.1)	7469 (5.9)	2462 (1.9)	7 (0–20)	-
Any treatment	142,272	19,250 (13.5)	61,794 (43.4)	38,930 (27.4)	15,634 (11.0)	6664 (4.7)	16 (5–35)	6.2 (6.1;6.4) [<0.001]
OAH or INAH	39,736	5019 (12.6)	17,035 (42.9)	11,004 (27.7)	4562 (11.5)	2116 (5.3)	16 (5–37)	7.9 (7.7;8.1) [<0.001]
INCS	22,577	3819 (16.9)	11,073 (49.0)	5325 (23.6)	1694 (7.5)	666 (2.9)	12 (4–27)	2.2 (1.9;2.5) [<0.001]
AzeFlu	12,755	2179 (17.1)	5903 (46.3)	3305 (25.9)	1101 (8.6)	267 (2.1)	13 (4–28)	1.5 (1.1;1.9) [<0.001]
INCS + OAH	23,600	2832 (12.0)	9953 (42.2)	6701 (28.4)	2805 (11.9)	1309 (5.5)	17 (6–38)	8.5 (8.1;8.8) [<0.001]
AzeFlu + other	22,204	3021 (13.6)	9789 (44.1)	6590 (29.7)	2170 (9.8)	634 (2.9)	16 (5–31)	3.5 (3.2;3.8) [<0.001]
INCS + OAH + other	18,111	1548 (8.5)	7374 (40.7)	6227 (34.4)	2159 (11.9)	803 (4.4)	20 (9–37)	8.1 (7.7;8.5) [<0.001]
Any OCS	2457	145 (5.9)	415 (16.9)	939 (38.2)	622 (25.3)	336 (13.7)	40 (21–59)	15.0 (14.1;15.9) [<0.001][b]
Others	220	6 (2.7)	62 (28.2)	71 (32.3)	47 (21.4)	34 (15.5)	37 (15–64)	-[c]

Abbreviations: AzeFlu, Azelastine-Fluticasone intranasal formulation; CI, confidence interval; INAH, intranasal antihistamines; INCS, intranasal corticosteroids; OAH, oral antihistamines; OCS, oral corticosteroids.

[a]Adjusted comparisons between each medication scheme vs. no treatment.

[b]Difference higher than the minimal important difference.

[c]Insufficient sample size for analysis to be performed.

2.7 | Analysis of the data

2.7.1 | Missing data

When responding to the MASK-air® daily monitoring questionnaire, no questions can be skipped and data are saved to the dataset only after the final answer. This precludes any missing data within each questionnaire.

2.7.2 | Analyses of the data

Categorical variables were described using absolute and relative frequencies, while continuous variables were described using medians and quartiles. For each medication scheme, we assessed the distribution of VAS global allergy symptoms.

We applied multivariable linear mixed-effects models,[14] modelling the association between VASs and medication schemes. In such models, random effects accounted for the users and their country (with users being tested within countries) and for the month of the year (crossed random effect in relation to users and countries). In other words, we clustered observations by the user, country and month. In addition, in those models, we adjusted for the following covariates: AIT use, the occurrence of asthma, baseline number of domains (among sleep, daily activities, work and functionality) impacted by AR as reported by the patient, baseline number of AR symptoms reported by the patient, patient's age and gender, baseline VAS values and the number of reported days (this latter adjustment was necessary as there was an imbalance in the number of days reported between the users who were treated or not treated with AIT). Random slopes were not included. These models allowed us to compute the adjusted average differences in VAS for each medication scheme compared to no treatment. Sensitivity analyses were performed restricted to data (i) from users providing at least 15 days of MASK-air® data (to deal with poor app compliance) and (ii) prior to 2020 (to assess if there were relevant differences when considering only data prior to the COVID-19 pandemic). Sub-analyses were also performed for (i) VAS on nose symptoms, on eye symptoms and on the impact of AR on work as dependent variables and (ii) days when users were under treatment with AIT vs. days without AIT.

We applied multivariable mixed-effects logistic regression models[14] to quantify the use of each drug class in co-medication. Such models displayed a similar structure and set of covariates to the aforementioned linear mixed-effects models. That is, we clustered observations by the user, country and month, and adjusted for AIT use, the occurrence of asthma, baseline number of domains impacted by AR, baseline number of AR symptoms as well as patients' age and gender. Exponentials of correlation coefficients were interpreted as odds ratio (OR).

Differences in VAS global allergy symptoms were interpreted considering the MID for such VASs, which we purposely determined in this study. The MID for VAS global allergy symptoms was determined based on distribution-based methods – we considered the MID to correspond to 0.5 × standard deviation of the baseline observations.[15] Based on such an approach, we estimated an MID of 11

(out of 100) points for VAS global allergy symptoms (as the standard deviation of baseline observations was 22). We used the term "MID" instead of "minimal clinically important difference", as some authors posit that the difference is more important to the patient than to the clinician.[16]

Estimated effect sizes were presented alongside 95% confidence intervals and two-sided *p*-values. The multiplicity of tests was accounted for using the Bonferroni correction. All analyses were performed using software R (version 4.0.0), with lme4 and lmerTest packages.

3 | RESULTS

3.1 | Demographic characteristics of the patients

We analyzed 269,837 days from 10,860 users (mean age ± SD: 38.2 ± 13.8 years). There were 177,067 (55.8%) observations from women. A total of 142,272 days (52.7%) involved the use of at least one medication (Figure S1 and Table S2).

3.2 | Frequency of medication use

Days with single medication involved OAH or INAH (39,736 days; 14.7%), INCS (22,577 days; 8.4%) or Aze-Flu (12,755 days; 4.7%). Days with co-medication involved INCS + OAH (23,600 days; 8.7%), INCS + OAH + other medication (18,111 days; 6.7%) and Aze-Flu + other medication (22,204 days; 8.2%) (Table 1).

3.3 | VAS global allergy symptoms in the full data set

3.3.1 | Median levels

The lowest median VAS levels (7/100) were found for days without any treatment, followed by days under INCS (12/100) or Aze-Flu (13/100) (Table 1). The highest median levels were found for OCS (40/100) and INCS + OAH + other (20/100) (Table 1).

3.3.2 | Adjusted models

In adjusted models, Aze-Flu and INCS displayed the lowest average difference in VAS when compared to no treatment (Table 1). The highest average difference was found for OCS, being the only difference higher than the MID (Table 1).

In addition, Aze-Flu was associated with lower adjusted average VAS global allergy symptoms than all other medication schemes (even though without significant differences when compared to INCS). These differences were higher than the MID in comparison to OCS (Table 2). OCS was associated with higher adjusted average VAS global allergy symptoms than all other medication schemes.

Similar results were obtained in sensitivity analyses restricted to MASK-air® users providing at least 15 days of data or to data prior to 2020 (Table S3).

3.3.3 | Comparisons considering allergen immunotherapy

Allergen immunotherapy was associated with a decrease in VAS global allergy symptoms both for days on which no treatment was used (average adjusted difference = −2.2; 95% CI = −3.4; −1.0) and for days with medication use (average adjusted difference considering medication of any type = −1.5; 95% CI = −2.6; −0.4) (Table 3; Figure S2). AIT did not associate with VAS differences higher than the MID.

3.4 | VAS on individual symptoms and work in the full data set

For VAS nose, VAS eyes and VAS work, results were similar to those of VAS global allergy symptoms (Figure 1; Table S4). The lowest average differences in VAS were observed for Aze-Flu and INCS, while the highest were observed for INCS + OAH (alone or with additional medications) and OCS.

3.5 | Frequency of co-medication among different drug classes in the full data set

Table 4 displays the chances that each medication class has of having been used in co-medication when compared to the remaining classes. The higher the OR, the higher the chances that this medication class was used in co-medication. Aze-Flu was the drug class with the lowest chances of being used in co-medication (OR = 0.75; 95% CI = 0.71–0.80; i.e., MP-AzeFlu was associated with a 25% decrease in the odds of being used in co-medication), followed by OAH (OR = 0.78; 95% CI = 0.75–0.81), INCS (OR = 0.90; 95% CI = 0.86–0.93), other rhinitis drugs (OR = 1.40; 95% CI = 1.33–1.48), INAH (OR = 2.41; 95% CI = 2.07–2.81) and OCS (OR = 7.26; 95% CI = 5.86–9.01).

3.6 | VAS global allergy symptoms in the first 2 weeks of reporting

The same ranking order was found for analyses restricted to day 1 or days 2–15 of MASK-air® use (Figure S3 and Table S5). However, for all medication schemes, median VAS global allergy symptom levels were substantially lower for days 2–15 than for day 1. The number of days with VAS ≥50/100 was also lower for days 2–15 than for day 1, although results differed depending on the drug classes (Table S5, Figures 2 and S4). From the best to the worst control, we identified

(i) no medication, (ii) monotherapy with INCS or Aze-Flu, (iii) Aze-Flu co-medication, (iv) OAH monotherapy and INCS co-medication and (v) OCS.

We observed that the differences in median VAS global allergy symptoms (when compared to "no treatment") were lower than the MID for INCS, Aze-Flu and Aze-Flu + other medication for all days. On the other hand, OAH, INCS comedication and OCS had a difference higher than the MID for 7–15 days. However, these are unadjusted differences.

4 | DISCUSSION

This study follows the results of previous MASK-air® studies showing differences between monotherapy and co-medication.[3–5] However, this is the first study to rank treatments using direct patient data from a real-life setting for AR, considering multiple treatments and AIT and adjusting for confounding factors using multivariable mixed-effects models.

The MASK-air® project follows a stepwise approach with continuous iterations using previous and novel data. All studies have brought novel data and interpretation. In this study, there is a new analysis using a multivariable mixed-effects model, allowing to control for several parameters of clinical relevance. Some findings are consistent with previous studies, but new findings have been identified (Table S6). Consistent findings with those of previous studies include the identification that AR control was better on days of monotherapy with INCS or Aze-Flu, worse on days of monotherapy with OAH, and the worst on co-medication days.[4,5] We confirmed that, except for OCS, monotherapy schemes were associated with lower VASs on global and specific AR symptoms than co-medication schemes. In particular, Aze-Flu was found to be the treatment associated with the lowest VASs and with the lowest chances of being used in co-medication. We have also confirmed that Aze-Flu is more often used alone than INCS.[4,5] While OAHs were also frequently used in monotherapy, this may be associated with the fact that OAHs are frequently used in patients with mild AR in whom they may be sufficiently effective (Table S6).

Novel findings were observed in this study. We found that AIT was associated with lower AR VAS[17] in untreated days, but that, for treated days, such an association was only observed in days under treatment with OAH/INAH or INCS. Since the sample size did not allow us to perform separate analyses assessing SLIT and SCIT, it is not possible to determine whether specific AIT schemes can be associated with improvements in days under treatment with other medication schemes. In this study, we also observed that, although patients receiving Aze-Flu are likely to have more severe AR than those treated with INCS,[18] VAS levels of Aze-Flu monotherapy days are lower for all symptoms and work impact than those of INCS. The same applies to co-medication. We also found that VAS eyes were lower in Aze-Flu monotherapy and co-medication than in INCS monotherapy and co-medication, respectively. This confirms the RCTs[19] but shows that the effect was observed both as monotherapy and co-medication. MIDs are patient-derived scores that reflect changes in a clinical intervention that is meaningful for the patient.[20] In this study, as suggested,[15] a close collaboration between statisticians and clinicians was used to determine the MID for VAS global. A major finding of the current study is that differences in VAS associated with INCS or Aze-Flu (monotherapy or with co-medication) use are lower than the MID when compared to no treatment, whereas

TABLE 2 Adjusted average differences in visual analogue scale (VAS) on global allergy symptoms (95% confidence intervals) [*p*-values] by medication scheme

	AzeFlu	INCS	OAH or INAH	AzeFlu + other	INCS + OAH	INCS + OAH + other
INCS	0.8 (−0.1;1.6) [0.070][a]	-				
OAH or INAH	4.1 (3.3;4.9) [<0.001]	4.2 (3.5;4.8) [<0.001]	-			
AzeFlu + other	5.1 (4.5;5.8) [<0.001]	0.7 (0;1.5) [0.060]	0.9 (0.3;1.5) [0.002]	-		
INCS + OAH	6.5 (5.3;7.6) [<0.001]	6.3 (5.8;6.7) [<0.001]	3.9 (3.4;4.4) [<0.001]	2.7 (1.9;3.5) [<0.001]	-	
INCS + OAH + other	5.7 (5.1;6.3) [<0.001]	7.5 (6.9;8.2) [<0.001]	5.9 (5.3;6.5) [<0.001]	4.0 (2.8;5.1) [<0.001]	−0.2 (−1.0;0.7) [0.690]	-
Any OCS	13.5 (11.8;15.2) [<0.001][b]	10.7 (9.4;12.0) [<0.001]	10.4 (0.8;11.9) [<0.001]	9.7 (8.3;11.2) [<0.001]	5.8 (4.4;7.2) [<0.001]	5.4 (4.0;6.7) [<0.001]

Note: The table presents results on the comparisons between medication schemes listed in each row vs. those listed in each column.

Abbreviations: AzeFlu, Azelastine-Fluticasone intranasal formulation; INAH, intranasal antihistamines; INCS, intranasal corticosteroids; OAH, oral antihistamines; OCS, oral corticosteroids.

[a]Interpretation (for illustrative purposes): INCS was associated with an adjusted average VAS of 0.8 points more than AzeFlu (95% confidence interval = −0.1;1.6; *p*-value = .070). On the other hand, AzeFlu was associated with an adjusted average VAS of 0.8 points less than INCS (95% confidence interval = −1.6;0.1; *p*-value = .070).

[b]Difference higher than the minimal important difference.

TABLE 3 Visual analogue scale (VAS) on global allergy symptoms by medication scheme for days under treatment with allergen immunotherapy (AIT) and days with no AIT

	Days under treatment with AIT			Days with no AIT			
	N days	Median VAS (P25-P75)	Average difference in VAS[a] (95% CI) [*p*-value]	*N* days	Median VAS (P25-P75)	Average difference in VAS[a] (95% CI) [*p*-value]	Difference in AIT use – Average difference in VAS (95% CI) [*p*-value]
No treatment	43,499	5 (0–16)	-	84,078	8 (0–23)	-	−2.2 (−3.4;-1.0) [<.001]
Any treatment	38,714	13 (4–29)	6.3 (6.1;6.6) [<.001]	103,564	17 (6–38)	6.2 (6.0;6.4) [<.001]	−1.5 (−2.6;-0.4) [.006]
OAH or INAH	9921	13 (3–29)	7.8 (7.4;8.1) [<.001]	29,816	18 (6–41)	8.0 (7.7;8.2) [<0.001]	−1.8 (−3.4;-0.1) [.041]
INCS	6360	10 (4–24)	3.1 (2.6;3.5) [<.001]	16,218	13 (4–28)	1.8 (1.4;2.2) [<.001]	−2.6 (−4.8;-0.4) [.021]
AzeFlu	3058	12 (3–22)	1.5 (0.9;2.2) [<.001]	9698	13 (4–31)	1.5 (1.0;1.9) [<.001]	−1.4 (−4.9;2.0) [.415]
INCS + OAH	6732	13 (4–31)	7.3 (6.7;7.8) [<.001]	16,869	19 (7–41)	8.9 (8.5;9.4) [<.001]	−1.2 (−3.6;1.1) [.298]
AzeFlu + other	5652	16 (6–27)	4.3 (3.8;4.9) [<.001]	16,553	16 (5–34)	3.1 (2.7;3.5) [<.001]	−0.7 (−3.7;2.2) [.614]
INCS + OAH + other	4825	20 (9–33)	8.5 (7.9;9.0) [<.001]	13,287	20 (9–39)	7.9 (7.4;8.4) [<.001]	−2.4 (−5.3;0.5) [.110]
Any OCS	395	27 (11–45)	-[b]	2063	43 (25–62)	21.2 (19.3;23.1) [<.001][c]	-[b]

Abbreviations: AzeFlu, Azelastine-Fluticasone intranasal formulation; CI, confidence interval; INAH, intranasal antihistamines; INCS, intranasal corticosteroids; OAH, oral antihistamines; OCS, oral corticosteroids.

[a]Comparisons between each medication scheme vs. no treatment.

[b]Insufficient sample size for analysis to be performed.

[c]Difference higher than the minimal important difference.

for all other schemes, differences were higher than the MID for at least 7 days. These, however, concern unadjusted differences. When considering results from mixed-effects models, clustering observations by the patient and adjusting for baseline variables, we only observe differences higher than the MID when comparing OCS vs. no treatment or OCS vs. Aze-Flu.

4.1 | Strengths and limitations

Interpretation of these results should consider the limitations of this study. Due to its cross-sectional nature, it is not possible to establish causality or directionality. The best way to analyze MASK-air® data has been carefully assessed by MASK-air methodologists. Initially, it was expected that patients would use the app regularly, and that longitudinal analyses could be done with large volumes of data. However, most patients use the app for a short period of time and intermittently,[21] so that longitudinal analyses can only be performed considering short periods of time and with smaller amounts of data.[4] Thus, in MASK-air, we used a cross-sectional approach, taking days as the unit of analysis instead of patients (although patients were used to cluster reporting days). This approach has been applied in many studies.[3,5,22–24] On account of the cross-sectional nature of MASK-air® data, it was not possible to determine whether MASK-air® patients mostly report VAS indicating the severity/control of their AR symptoms (i) prior to medication use or (ii) after medication use (i.e., we are not able to know if medication associated with better AR control displayed such association because they were used for milder symptoms or because they were more effective). A proper assessment of the effectiveness of the different drug classes and medication schemes would require patients to report VAS both prior to and after medication use. To partly overcome these limitations, we (i) not only assessed differences in VAS but also evaluated the frequency with which each drug class was used in co-medication (patients tend to use co-medication when feeling worse, as observed in previous studies; therefore, co-medication may be an indirect marker of worse AR control as it suggests that the severity of AR symptoms was such that patients were prompted to use more than one medication) and (ii) adjusted for patients' baseline VAS and domains impaired by AR (as a proxy of AR severity).

In this study, we did not consider asthma medication, which may possibly have some influence on AR symptoms according to the one-airway one-disease hypothesis. Nevertheless, we believe the eventual effect of asthma medication to be non-differential across AR medication groups.

There are also limitations in the way AIT is reported. The MASK-air® questionnaire does not differentiate between products, and we did not perform separate analyses for AIT types, as there is a relatively low number of days for some AIT types (e.g., sublingual AIT with tablets) for many medication classes. We were also not able to consider indirect evidence when comparing the different medication classes, given a possible violation of the transitivity assumption.

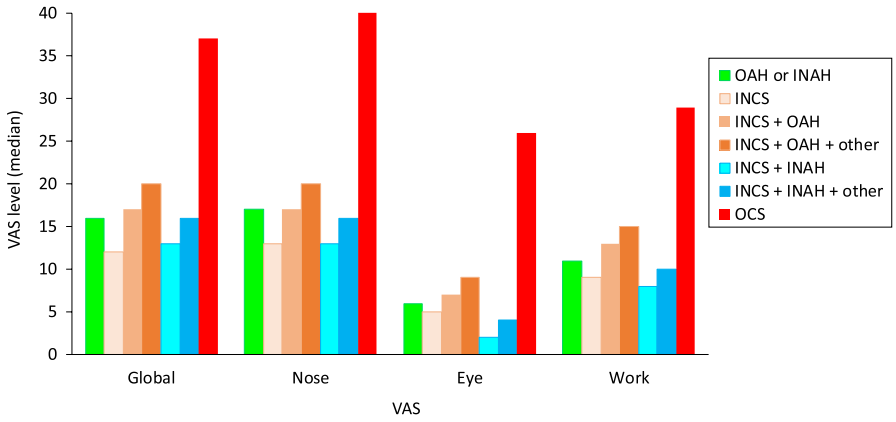


FIGURE 1 Median visual analogue scale (VAS) levels for global allergy symptoms, nose symptoms, eye symptoms and impact of allergic rhinitis on work. INAH, intranasal antihistamines; INCS, intranasal corticosteroids; INCS+INAH, Azelastine-Fluticasone; OAH, oral antihistamines; OCS, oral corticosteroids

TABLE 4 Chances that each medication class is used in co-medication compared to the remaining medication classes

	OR (95% CI) [*p*-value]
AzeFlu	0.75 (0.71–0.80) [<.001]
OAH	0.78 (0.75–0.81) [<.001]
INCS	0.90 (0.86–0.93) [<.001]
Other rhinitis drugs	1.40 (1.33–1.48) [<.001]
INAH	2.41 (2.07–2.81) [<.001]
OCS	7.26 (5.86–9.01) [<.001]

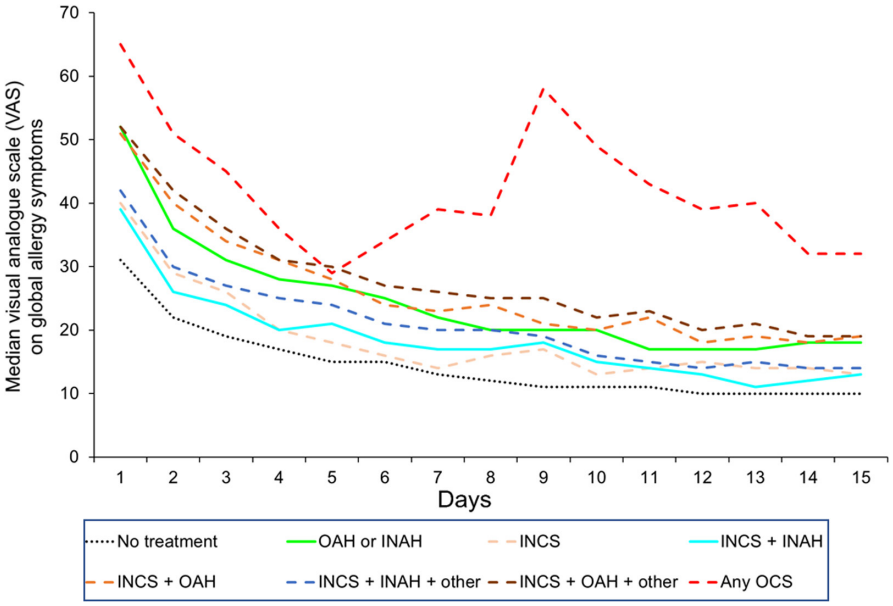
Abbreviations: AzeFlu, Azelastine-Fluticasone intranasal formulation; CI, confidence interval; INAH, intranasal antihistamines; INCS, intranasal corticosteroids; OAH, oral antihistamines; OCS, oral corticosteroids; OR, odds ratio that each medication class is used in co-medication when compared to the remaining medication classes.

Another limitation concerns the possibility of information biases, as MASK-air® information is self-reported. This is particularly relevant when registering medication. For instance, there may be errors in medication reporting or, due to how medication use is registered in MASK-air® (on a scroll list that differs across countries), medication bought in countries different from the one the user lives in may frequently end up not being reported. Finally, there is the possibility of selection biases, as there may be an overrepresentation of young adults, patients more concerned about their health and patients who are better treated. We do not have any information on the patients' ease of access to health care, which may be a factor conditioning drug and AIT choices. Despite such concerns, we observed that the seasonality of reported symptoms and of reported medication patterns in MASK-air® may not be dissimilar to those of the general population. In addition, the higher VAS levels on day 1 suggest that, despite relatively low median VAS levels, MASK-air® users are not necessarily patients with mild rhinitis.

This study also has important strengths. While some residual confounding may occur, we performed adjusted analyses considering relevant clinical and demographical variables. We built multivariable mixed-effects models so as to cluster observations by patients and adjust associations for several variables, to try to reduce confounding and to take into account differences in the number of reported days. Such an approach differentiates this study from others using MASK-air® data. In addition, results were obtained following the analysis of a large volume of direct patient data, with the structure of MASK-air® precluding the existence of missing data within each daily questionnaire response. Analyzed data were obtained using a very simple daily assessment tool (VAS) on a mobile phone. Finally, MASK-air® VASs have been assessed on their validity, intra-rater and test–retest reliability and responsiveness,[25] while the VAS cutoffs used concern those of ARIA classes,[26] which have been used in several previous studies.

5 | CONCLUSIONS

This unique study will impact guidelines. The major gap in guidelines is that of how the patients behave in real life. This study enables, for the first time, the development of big-data-driven, digitally-enabled, patient-centred next-generation guidelines embedding information from direct patient data on monotherapy, co-medication and AIT into GRADE-based evidence synthesis and guidance (e.g., ARIA, Practice Parameters) including the MID, so as to devise recommendations which are simultaneously effective and capable of being followed by patients and clinicians. One of the major outcomes of MASK-air® raises the hypothesis that the efficacy of medications cannot be appreciated using medications or AIT alone, but needs a global evaluation. Four types of studies are now needed, including (i) studies combining direct patient data with allergen and pollution exposure to check whether the patterns found in the present study are confirmed during seasons associated with a high risk of AR worsening, (ii) adequately powered AIT studies testing different allergens and modes of administration, (iii) studies using unsupervised learning approaches to assess patterns of medication use in relation to the AR phenotype (intermittent vs. persistent disease and severity), as well as patterns of multimorbidity (patients with single or several allergic respiratory diseases can react differently) and (iv) confirmatory studies with sufficiently powered RCTs. While this approach is being followed for AR, it may be adapted and applied for asthma and other chronic diseases.



	Days				
	1	2	3	4 to 7	8 to 15
OAH or INAH	■	■	■	■	
INCS					
INCS + INAH					
INCS + OAH	■	■	■	■	
INCS + INAH + other					
INCS + OAH + other	■	■	■	■	■
Any OCS	■	■	■	■	■

■ MID: VAS>11 compared to no treatment

N=10,860 patients

FIGURE 2 Data on the visual analogue scale on global allergy symptoms for the first 2 weeks of reporting MASK-air® data. AzeFlu, Azelastine-Fluticasone; INAH, intranasal antihistamines; INCS, intranasal corticosteroids; OAH, oral antihistamines; OCS, oral corticosteroids

AUTHOR CONTRIBUTION

BSP performed the analysis and wrote the paper in collaboration with JB. JB proposed the study, analyzed the data and wrote the paper in collaboration with BSP. HS, JA, AB, WC, AS, TZ and JAF participated in the planning of the study. ASS, RJV, RA, DKC and PE participated in the analysis of the study. LK, OP, LB, VK, DLL, YO, MTV, VC, PCM, LC, CC, AAC, WJK, BG, TH, JCA, PK, HK, MM, RM, MMA, RM, MN, NGP, VP, NPT, FSR, SR, PWR, BS, MS, ATB, LTB, STS, JS, SW, AY and MZ proposed the app to their patients who voluntarily and in a fully anonymized fashion downloaded the app. IA, IJA, KCB, SBA, YB, GWC, TC, TC, EMC, SDG, PD, ZI, MJ, IK, MK, DL, BL, RL, JM, IT, AV, OV and DW are members of the MASK-air Think Tank. All authors revised the paper and agreed to its publication.

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CONFLICT OF INTEREST

IA reports personal fees from Roxall, Menarini, UCB, Faes Farma, Sanofi, Bial, Amgen, Abbott, Bayer, Organon. SBA reports grants from TEVA, personal fees from TEVA, AstraZeneca, Boehringer Ingelheim, GSK, Sanofi, Mylan. JB reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, personal fees from Purina, other from MASK-air. VC reports personal fees from Thermofisher. PCM reports personal fees from Abbvie, AZ, Bial, GSK, Mylan, Medinfar, Novartis, Sanofi. LC reports personal fees from Malesci, Menarini, Astra Zeneca, Novartis. AC reports grants and personal fees from Astrazeneca, GSK, Sanofi, personal fees from Boehringer-Ingelheim, Chiesi, Glenmark, Novartis, personal fees from Mylan, Abdi-Ibrahim. PD reports personal fees and non-financial support from Stallergenes Greer, ALK-Abello, Astra Zeneca, CHIESI, MYLAN/Meda Pharma, Novartis, GlaxoSmithKline, Sanofi, IQVIA personal fees from MENARINI. JAFonseca reports participation in SME that has mHealth technologies for patients with asthma. JCI reports personal fees from Abbott Ecuador, Bago Bolivia, Faes Farma, Laboratorios Casasco, Sanofi. LK reports grants and personal fees from Allergopharma, LETI Pharma,MEDA/Mylan, Sanofi, personal fees from HAL Allergie, Allergy Therapeut., Cassella med, grants from ALK Abelló, Stallergenes, Quintiles, ASIT biotech, Lofarma, AstraZeneca, GSK, Inmunotk, and Membership: AeDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV, GPA, EAACI. VK reports other from Norameda, BerlinCHemie Menarini. PK reports personal fees from Adamed, AstraZeneca, Berlin Chemie Menarini, Boehringer Ingelheim, Chiesi, GSK, Novartis, Polpharma.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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