LETTER TO THE EDITOR

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

To The Editor,

Allergen immunotherapy (AIT) is effective in allergic rhinitis (AR) and/or asthma. Randomized controlled trials (RCTs) have demonstrated the efficacy and safety of both subcutaneous (SCIT) and sublingual (SLIT) immunotherapy in patients allergic to pollen and house dust mites. 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.

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.

1 | METHODS

All MASK-air® data from 21 May 2015 to 6 December 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.

2 | 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 AIT median global symptoms VASs were lower 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 (Table S1).

3 | CONCLUSIONS AND LIMITATIONS

This POC study 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. 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).

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

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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.

CONFLICT OF INTEREST

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

| Medication scheme | N observations (%) | Symptoms VAS – median [95%CI] (IQR) |
|-------------------|--------------------|-----------------------------------|
|                   | AIT                | No AIT                            | p value       |
| 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) | <0.001 |
|                   |                    |                                   | 14 [14–15] (28) | <0.001 |
| Co-medication     | 5904 (10.9)        | 48,397 (88.1)                     | 17 [16–18] (31) | <0.001 |
|                   |                    |                                   | 20 [19–20] (35) | <0.001 |

TABLE 2 Differences in VAS global symptoms during and outside of the expected pollen season in the European data set of MASK®

| Medication scheme | N observations/days (N users) | VAS day 1 – median [p25-p75] | VAS all days – median [p25-p75] |
|-------------------|-------------------------------|-----------------------------|----------------------------------|
| FF                |                               |                             |                                  |
| MPAzeFlu          |                               |                             |                                  |
| MF                |                               |                             |                                  |
| OAH mono          |                               |                             |                                  |
| No treatment      |                               |                             |                                  |
| During pollen season |                           |                             |                                  |
| N observations/days (N users) | 3286 (331) | 50 [28–71] | 26 [8–50] |
| VAS day 1 – median [p25-p75] | 2594 (159) | 52 [25–73] | 16 [6–38] |
| VAS all days – median [p25-p75] | 4093 (351) | 50 [30–75] | 19 [7–39] |
| Outside pollen season |                           |                             |                                  |
| N observations/days (N users) | 1116 (99) | 44 [19–67] | 19 [5–44] |
| VAS day 1 – median [p25-p75] | 1258 (80) | 34.5 [15–62] | 18 [7–36] |
| VAS all days – median [p25-p75] | 1437 (95) | 46 [17–64] | 14 [5–34] |

Note: 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.

Abbreviations: FF, Fluticasone furoate; MF, Mometasone furoate; MPAzeFlu, Azelastine-Fluticasone Propionate; OAH, Oral antihistamines; p25-p75, percentile 25-percentile 75; VAS, Visual analogue scale (assessing the severity of overall allergic symptoms on that day).
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