Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study

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Short title: Treatment of allergic rhinitis using an App

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Abstract

Background: Mobile health may be used to generate innovative insights into optimizing treatment to improve allergic rhinitis control.

Objectives: A cross-sectional real world observational study was undertaken in 22 countries to complement a pilot study and bring novel information on medication use, disease control and work productivity in everyday life of patients with allergic rhinitis.

Methods: A mobile phone app (*Allergy Diary*, freely available Google Play and Apple stores) was used to collect data of daily visual analogue scales (VAS) for (i) overall allergic symptoms, (ii) nasal, ocular and asthma symptoms, (iii) work, as well as (iv) medication use using a treatment scroll list including all allergy medications (prescribed and over-the-counter (OTC)) customized for 22 countries. The four most common intra-nasal medications containing intra-nasal corticosteroids and eight oral H1-antihistamines were studied.

Results: 9,122 users filled in 112,054 days of VAS in 2016 and 2017. The assessment of days was informative. The control of days with rhinitis differed between no [best control], single [good control for intranasal corticosteroid-treated days] or multiple treatments [worst control]. Users with the worst control increased the range of treatments being used. The same trend was found for asthma, eye symptoms and work productivity. Differences between oral H1-antihistamines were found.

Conclusions: This study confirms the usefulness of the *Allergy Diary* in accessing and assessing patient behavior in allergic rhinitis. This observational study using a very simple assessment tool (VAS) on a mobile phone had the potential to answer questions previously thought infeasible.

Capsule summary

Most rhinitis patients use on-demand treatment when they are not controlled. Control was worse with increasing medications. Real life data may not be aligned with guidelines.

Clinical implications

A behavioural disconnection was found in the study since patients are not adherent to treatment and treat themselves on-demand when they are not controlled whereas the vast majority of physicians prescribe long-term treatment to achieve control. Shared-decision making is essential.

Key words

Allergic rhinitis, anti-histamines, asthma, conjunctivitis, corticosteroids, mobile health, MASK, treatment

Abbreviations

AR: Allergic rhinitis
AzeFlu : Intranasal azelastine-fluticasone propionate
CET : Cetirizine
DL: Desloratadine
FEXO: Fexofenadine
FF: Fluticasone Furoate
FP: Fluticasone Propionate
INCS: Intranasal corticosteroid
INN: International Nonproprietary Names
LEVOCET: Levocetirizine
Lora: Loratadine
MASK-rhinitis (Mobile Airways Sentinel NetworK for allergic rhinitis)
Mometasone Furoate (MF)
OAH: Oral H^1-anti-histamine
RCT: Randomized controlled trial
visual analogue scales (VAS)

Introduction

The treatment of allergic rhinitis (AR) is complex as many drugs are available in oral and/or topical formulations. Many guidelines for AR are evidence-based and have led to a better management of AR. However, guidelines are mostly based on randomized controlled trials (RCTs), typically undertaken on highly selected populations, often with limited/unclear generalizability to routine care contexts (1, 2). They propose to increase treatment to achieve disease control (i.e. sleep, social and school/work impairment) that is the ultimate aim of the treatment. Intra-nasal corticosteroids represent the most effective AR treatment for most patients, but their effect is relatively slow, taking several hours (3) and many patients prefer oral medications. A formulation of fluticasone propionate (FP) and azelastine (AzeFlu) is more effective than INCS alone (4) and has the advantage of acting within minutes (5). Patients are poorly adherent to treatment and often self-medicate (6, 7). They want more effective and fast acting treatments. Observational real-life studies are therefore needed to complement RCTs in order to better understand the efficacy of INCS-containing medications since they do not select patients and report their behavior.

MASK-rhinitis (Mobile Airways Sentinel NetworK for allergic rhinitis), an information and communications technology (ICT) system centered around the patient (8-12) operational in 23 countries, uses a treatment scroll list including all medications customized for each country and a visual analogue scales (VAS) to assess rhinitis control. A pilot study in over 2,900 users allowed differentiation between treatments (13). Patients did not necessarily use treatment on a daily basis in a regular way but appeared to increase treatment use when their symptom's control worsens. However, the pilot study needs to be confirmed with a larger number of users and more medications tested.

The present cross-sectional observational study was undertaken in 9,122 users in 22 countries (data collection was just started in Argentina) to confirm the pilot study (13) using the same methods and to bring novel information on medication use, and associated disease control, work productivity (14) and allergic multimorbidity (13). The study was focused firstly on the four most commonly used intra-nasal medications containing intra-nasal corticosteroids: Fluticasone Furoate (FF), Fluticasone Propionate (FP), Mometasone Furoate (MF) and AZeFlu. We did not perform the same analysis with oral H1-antihistamines as they are often associated with INCS and many patients would have been analysed twice. In the second analysis, we examined some widely used oral H1-antihistamines: Bilastine, Cetirizine (CET), Desloratadine (DL), Ebastine, Fexofenadine (FEXO), Levocetirizine (LEVOCET), Loratadine (Lora) and Rupatadine. In the first analysis, we compared days with single treatment with days with multiple treatments. In the second analysis, we just used days with a single treatment.

Methods

Users

All consecutive users from January 1, 2016 to December 31, 2017 were included with no exclusion criteria according to methods previously described (13, 14).

Setting

Users from 22 countries filled in the *Allergy Diary* (Table 1). Data collection was just started in Argentina and not included

Ethics

The Allergy Diary is CE1. CE marking is a certification mark that indicates conformity with health, safety, and environmental protection standards for products made in the EU and meets the essential requirements of all relevant European Medical Device Directives (15). CE1 includes sterile and non-sterile products and assess whether the device has a measuring function.

The data were anonymized including data related to geolocalization using k-anonymity (16).

An independent Review Board approval was not required since the study is observational and users agreed to have their data analysed (terms of use).

Allergy Diary

Geolocalized users assess their daily symptom control using the touchscreen functionality on their smart phone to click on five consecutive VAS scores (i.e. general, nasal and ocular symptoms, asthma and work). Users input their daily medications using a scroll list which contains all country-specific OTC and prescribed medications available for each country (Figure 1 online). The list has been populated using IMS data.

Days reported by users included days with or without treatment.

The present study is another *Allergy Diary* study. Some of the raw data used in the first paper (up to November 2016) (13) were used in this study, but analyses differed.

Selection of medications

The International Nonproprietary Names (INN) classification was used for drug nomenclature (17). Monotherapy was defined as days when only one single medication for rhinitis was reported. AzeFlu 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 for rhinitis. Asthma medications were not considered in co-medication.

Size of the study

In this study, all registered users were included to obtain the best possible estimates for the specified time window. From the pilot study, numbers tested largely exceed those needed to find significant differences in the full set analysis (13). However, we did not consider medications with a sample size under 1,000 days of reporting.

Statistical methods

A non-Gaussian distribution was found for the data. Non-parametric tests and medians (and percentiles) were used. Correction for multiple testing was made when appropriate.

Some users reported VAS scores more than once a day. In the pilot study, we found that the highest reported value should be used and we followed this study (13). We however tested in an exploratory analysis VAS levels in duplicates and multiplicates.

Analysis of the data

We conducted, as previously published (13), separate analyses using the full-set of data and data on just the first day of reporting.

In the first analysis, only users who reported no treatment or treatment by the intra-nasal FF, FP, MF and AZeFlu were studied (Figure 2 online). Those receiving other INCS were excluded. For co-medication, we initially selected second generation oral H1-antihistamines (OAH): CET, DL, Ebastine, FEXO, LEVOCET, LORA and Rupatadine (Group + OAH). There are many other OAH, but we did not consider them since their pharmacologic properties vary widely and they were not often used. We considered two other groups in INCS users for co-medication: users who reported OAH and another medication (Group OAH + other) and users who reported another medication (+ Other). Users who reported other medications but no INCS were not analyzed. As a primary end point, using the full data set, we studied median VAS global measured (“Overall how much are your allergic symptoms bothering you today?”) levels for

days with FF, FP, MF and AZeFlu and for days without medications. The primary and secondary end points were analyzed using the Kruskal-Wallis test and Wilcoxon and Mann-Whitney test with Dunn-Bonferroni's post hoc analysis to correct for multiple testing. Moreover, we analysed the data using three cutoffs: VAS <20/100 (controlled days), VAS 20-49 (days with moderate control), VAS ≥50 (days with poor control) according to a consensus (18) and available data of the pilot study (13, 14). The same analyses were conducted for the first day of VAS report. Secondary end-points included VAS eye, asthma and work.

In the second analysis, we compared days with monotherapy for the most common OAH: CET, DL, Ebastine, FEXO, LEVOCET, LORA and Rupatadine monotherapy. We did not consider other OAH with a sample size under 1,000 days (or close to this number). We only compared VAS global measured. The mean number of days of reporting was considered for each treatment.

We then performed exploratory analyses to investigate whether there are temporal patterns in the reporting of VAS in the app users. We assessed the VAS levels on: (i) days with more than 1 VAS reported, (ii) the first day of reporting and first day of new reporting in users with non-consecutive data, (iii) days without treatment followed by a day with treatment and (iv) days with treatment followed by a day without treatment.

Results

Demographic characteristics

The study included 9,122 users. Roughly 5% of users did not report their age and were ascribed to "zero". Users ranged in age from zero to 92 years (mean, SD: 32.4 ± 15.2 years). There were 54.7% women and 45.3% men. The age repartition is given in Figure 3 online.

A total of 112,054 days was recorded. Duplicates or multiplicates for the same day were found in 14,767 days. Global VAS was not recorded in 754 (0.8 %) days with App data reported. There were 52,706 (54.6%) days without treatment and 18,117 days with the targeted INCS (Figure 1).

Analysis of VAS global measured

On visual inspection, no clear trajectory of VAS could be easily identified, as users reported erratically their VAS and treatment data. Figure 4 online reports trajectories for French users as an example.

In the figure each user is identified by a member identifier number (vertical axis) and each user's trajectory is represented horizontally by dots - each dot representing a day of VAS recording).

Results are reported in Table 2, Figures 2 and 3.

Analysis of VAS global measured on days without treatment and days with INCS treatment

The first day of reporting, VAS levels were reported by 4,991 users without treatment, 1,395 users with OAH and 1,281 users with INCS treatment (Table 2). The percentage of users with single treatment ranged from 34.0% (FP), 39.2% (MF), 40.5% (FF) and 59.6% (AzeFlu). Days with INCS alone had similar median VAS levels (35 to 44).

For the full data set of 96,533 days, VAS levels were reported by 6,236 users without treatment, 3,664 users with OAH and 2,575 users with INCS treatment (Table 2). Monotherapy was reported 45 to 55% of the days (FF or MF versus AzeFlu – Figure 2). For monotherapy, median VAS levels ranged from 5 (FF) to 23.5 (FP). For day 1 and the full data set, the same trend was found in INCS treated users: lowest median levels were found for monotherapy, increased levels with co-medication by OAH and highest levels for co-medication with OAH + other treatments (Figure 3). Variable levels of VAS were observed for co-medication with other treatments. The numbers of days of co-medication with another INCS are too low to make any comparison (Table 2).

Analysis of VAS global measured on days with OAH treatment alone

The first day of reporting, days with no treatment or those with INCS in monotherapy had similar median VAS levels (34 to 44). On the other hand, there were some variations for OAH in monotherapy. LEVOCET days had a median VAS level intermediate between untreated or INCS-treated days and the other OAH. For the full data set of 96,533 days, median VAS levels of days with INCS were lower than those of days with OAH but Bilastine, FEXO, LEVOCET and Rupatadine had levels similar to those of INCS (Table 2).

Apart from days with FP treatment (low numbers), the mean numbers of days of reporting medications per user ranged from 4.00 (CET) to 8.98 (AzeFlu).

Analyses of VAS for eye, asthma and work

Analyses of VAS eye, asthma and work are reported in Figures 5A, B and C online supplement. Trends for the three secondary end points are similar to those of VAS global measured, i.e. low median levels similar to untreated days for the single treatment, increased levels with co-medication by OAH and highest levels for co-medication with OAH + other medication, and the

highest percentage of users with single treatment observed for AzeFlu. Fewer users reported VAS work, but the trends were similar.

Exploratory analyses investigating potential temporal patterns in the reporting of VAS

Assessment of duplicates or multiplicates for day 1

Days with 2 or more VAS levels reported at least 1 hour apart within the same day were selected. The dataset included 1,576 days for VAS global measured. A significantly higher VAS was found at second reporting compared to the first. When the data were stratified by the type of treatment recorded at first entry (no treatment, AzeFlu FF, MF and FP), these findings were only significant for days with no treatment. No difference was found for days with (any) treatment (Table 1 online).

VAS levels depending on consecutive and non-consecutive data

There were 4,132 users with at least two non-consecutive calendar days of VAS reported (n=89,473 days in total). The global VAS levels measured on day 1 were found to be significantly higher when compared to the global VAS levels measured on the first day of new reporting (i.e. or first non-consecutive calendar day reported), regardless of the presence/type of treatment (Table 3).

The distribution of global VAS on the 391 consecutive couple of calendar days consisting of a day without treatment followed by a day with treatment showed a non-significant increased level in treated days (median [p25-75] =23 [11-49] to 28 [14-50], (p=0.07, Wilcoxon W test).

The distribution of global VAS on the 350 consecutive couple of calendar days consisting of a day with treatment followed by a day without treatment showed a significant decreased level in untreated days (median [p25-75] =23 [13-45] to 20 [9-38], (p=0.01 Wilcoxon W test).

Discussion

A pilot study using a very simple assessment (VAS) on a cell phone in 2,871 users who filled in 17,091 days suggested that an App may give novel information concerning the treatment of AR (13). However, the sample size was possibly too small to draw definite conclusions. This study in a larger sample (9,111 users in 22 countries, 97,287 days) confirms the findings of the pilot study showing that, in real life, the assessment of days can inform on patient's treatment and bring novel insight on the behaviour of AR patients towards treatment and novel concepts for change management of AR (19). The control of days differs between no treatment (best

control), single treatment or co-medication (worst control). This study showed for the first time that the same trends were observed for global symptoms, ocular symptoms, asthma and work productivity. This study suggests contrary behaviour between physicians and patients since the range of treatments was increased in those with poor control whereas, according to guidelines, physicians are recommended to increase the treatment to achieve control. This major gap in AR treatment may explain the overall low level of satisfaction of severe AR patients reported in many studies.

Strengths and limitations

The current study has many strengths including larger numbers, multiple countries, range of treatments studied and patient/person-generated data.

As for all studies using participatory data, potential biases include (i) the likelihood of sampling bias likely present, difficult to assess generalizability of the study, (ii) outcome misclassification that cannot be assessed and, by definition due to ethical problems, there very little information on patient (or day) characteristics. App users are not representative of all patients with rhinitis. The issue of potential selection bias was limited by the fact that we considered days and not patients in the analyses.

As in other studies (13, 20), we used days in a cross-sectional analysis because there is no clear pattern of treatment and a longitudinal study was not feasible since users mostly use the App intermittently. Although this observation may differ from RCTs, our study is a real-life approach.

For this study, other biases should be considered. The diagnosis of AR was not supported by a physician but was a response to the question: “Do you have allergic rhinitis? Yes/No”. There may therefore be some users with non-allergic rhinitis who may have responded “Yes” to the question. There are potential measurement biases when using apps including collection of information, education of the patient, availability and ability to use a smartphone (13). Users self-identified themselves as having AR without confirmation of the diagnosis. Precise patient characterization is impossible using an App, but every observational study using the *Allergy Diary* was able to identify days with poor control or criteria of severity (20-24). Adherence to treatment is impossible to prove as users do not report data all days and users may not report all medications used. Nonetheless, mobile technology is becoming an important tool to better understand and manage AR and brings novel information that were not available with other methods (20-26).

Asthma was assessed using a single VAS largely validated in rhinitis (27). In asthma, VAS was shown to be an effective measure of control (28). In the present study, we did not investigate specific symptoms or perform any pulmonary function test. Thus, it is possible that some users may have misunderstood the question or overestimated the disease. However, the results are extremely consistent.

We only considered days and not patients' trajectories because these are highly variable, patients using auto-medication depending on AR control as previously shown (13).

Longitudinal capture is very challenging with this App but this appears to be the case for all Apps. Patient's engagement with digital health in real world scenarios is usually lower than in RCTs. Although this is a limitation in relation to causal inference, it suggests that a new methodological approach is needed. It appears that treatment trajectories are specific for almost each user and most users have gaps in their treatment when they are well controlled.

Interpretation of the results and generalizability

This real world assessment of the *Allergy Diary* using VAS allows assessment of treatment efficacy by days, which represents real-life estimation of AR control and likely reflects real-life better than patients' assessments at regular intervals since (i) it is known that AR is a highly variable disease, and control varies widely between days in relation to allergen and environmental exposure, (ii) patients are rarely adherent to their treatment, (iii) patients often stop treatment when they feel better and (iv) patients increase their treatment when uncontrolled.

VAS scores were greater on days with treatment than on days without treatment. This study confirms the study of the pilot one (13) in which, median VAS levels on days without treatment were similar in users who never reported any medication use and in those who were occasionally treated. Moreover, in a small sample, it was found that consecutive days under treatment are less well controlled than days without treatment. In INCS-treated users, days with a single treatment were better controlled than days with multiple treatments. An important message from this paper is that, overall, in real life, patients treat themselves when they suffer from symptoms and stop their treatment when they are controlled. This accords with previous data (29, 30). This study, using objective data, confirmed that adherence is poor. Most AR patients may have mild and/or intermittent disease that does not need a regular treatment to achieve control. The concept of pro-active medication and patient participation (31) - the patient starting treatment when experiencing symptoms and continuing for a few days after getting control - may be of great interest and could be tested with the App. In asthma, self-guided

treatment was found to be of interest (31-33). Such real-life findings may ultimately affect the way in which guidelines are constructed to align them more with human behaviour. We have already initiated a program entitled Change management in rhinitis and asthma (19) in which we propose to develop next-generation care pathways and test the recommendations of GRADE guidelines in AR (3, 4) according to real-world evidence using data of MASK. A first meeting was held at the Pasteur Institute, Paris (December 3, 2018) to provide guidance for their development.

This observational study made it possible to differentiate OAH and INCS, confirming known data, (34) and was able to differentiate between OAH. LEVOCET was found to be the most effective OAH confirming clinical experience. On the other hand, CETI appeared not to have been as effective. However, there were a large number of generics for CETI and this could be studied when more users will be available. This study could also differentiate the three medications containing INCS: FF, MF and MP-AZeFlu and confirm previous studies (35)(36) extending our understanding of how AR treatment is used. RCTs showed that MP-AzeFlu is more effective than single components available in pharmacies (37) or components using the same formulation (38).

The same trends for INCS-containing medications were observed for VAS global measured, eye, asthma and work. However, the percentages of well-controlled, controlled and poorly-controlled days differed indicating the independence of data already observed. Moreover, data on work are extremely important to facilitate an economic evaluation of treatments.

An important result is that VAS on day 1 was higher than any other consecutive/non-consecutive day. This indicates that patients start using the App when symptoms are uncontrolled. This is one specificity of analysing app data and should be considered in studies that assess the control of allergic diseases in relation to risk factors such as air pollutants and allergen exposure.

Conclusions

Real world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions supporting clinical trial designs and observational studies to generate innovative and new treatment approaches. These data hold potential to answer questions previously thought infeasible (39) such as the true patient's attitude towards treatment. This observational study shows highly consistent results between different outcomes (VAS levels) and brings novel concepts for the management of allergic diseases. When the patient experiences increased symptom, indicating a loss of control, he/she increases the number of medications used that day.

A total behavioural disconnection was found since most patients treat themselves on-demand when they are not controlled whereas the vast majority of physicians prescribe long-term treatment to achieve control. Shared decision making may offer a more rewarding approach AR management. The results of this paper will be of importance for the implementation of the MASK Good Practice recently recognized by DG Santé.

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692 **Table 1. Country and number of users recording Visual Analogue Scale score using the**
693 ***Allergy Diary* in the full data set**

694

Country	VAS measurements (days)				
	1	2 to 7	8 to 14	>14	Total
Austria	226 (56.6%)	121	16	36	399
Australia	49 (49.0%)	30	10	11	100
Belgium	48 (49.5%)	35	5	9	97
Brazil	572 (55.9%)	323	67	62	1024
Canada	6 (35.3%)	7	3	1	17
Czech Republic	1 (20.0%)	0	1	3	5
Denmark	37 (45.1%)	29	4	12	82
Finland	117 (44.8%)	93	25	26	261
France	319 (61.3%)	147	19	35	520
Germany	208 (39.8%)	141	35	139	523
Greece	47 (23.7%)	43	24	84	198
Italy	554 (44.6%)	389	87	213	1243
Lithuania	59 (17.7%)	89	52	134	334
Mexico	101 (13.0%)	207	128	343	779
Netherland	167 (53.9%)	94	23	26	310
Poland	286 (54.9%)	159	28	48	521
Portugal	647 (49.2%)	505	64	100	1316
Spain	129 (30.5%)	124	53	117	423
Sweden	33 (39.3%)	34	6	11	84
Switzerland	247 (64.0%)	111	11	17	386
Turkey	81 (52.6%)	42	10	21	154
UK	148 (42.8%)	104	46	48	346
Total	**4082 (44.7%)**	**2827 (31.0%)**	**717 (7.9%)**	**1496 (16.4%)**	**9122**

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Table 2: Results of VAS global measured

		Day 1		Full set (96,533 days)		
		N days	Median [p25-p75]	N days [users]	Median [p25-p75]	Mean number of days per user
No treatment		4991	34 [10-60]	52706 [6236]	8 [0-26]	8.45
Bilastine*		128	48 [19-69.5]	1563 [261]	16 [6-37]	6.00
Cetirizine*		350	52 [28-70]	2169 [545]	22 [9-50]	4.00
Desloratadine*		300	50 [26-71]	2085 [504]	21 [8-46]	4.14
Ebastine*		115	50 [26-72]	980 [201]	23 [9-48]	4.88
Fexofenadine*		112	55 [32.5-71.5]	1128 [183]	14 [8-35]	6.17
Levocetirizine*		149	43 [16-67]	1512 [260]	14 [5-28]	5.81
Loratadine*		175	49 [28-72]	1680 [344]	21 [10-39]	4.88
Rupatadine*		66	49 [23-63]	1138 [146]	18 [5-36]	7.69
FF		176	35 [19.5-58.5]	2182 [336]	5 [0-27]	6.49
	+ OAH	129	51 [22-66]	1317 [247]	21 [4-45]	5.33
	+ OAH + other	38	64 [49-77]	307 [80]	48 [24-63]	3.84
	+ other (no OAH)	84	53.5 [28-72]	968 [168]	23 [9-47]	5.76
	+ other INCS	7	50 [4-90]	113 [16]	61 [26-95]	7.06
AzeFlu		155	37 [16-60]	2722 [303]	13 [3-29]	8.98
	+ OAH	49	58 [40-73]	994 [113]	17 [7-40]	8.72
	+ OAH + other	12	54 [26-80]	174 [33]	31 [9-60]	5.27
	+ other (no OAH)	37	40 [21-65]	871 [98]	22 [11-42]	8.89
	+ other INCS	7	50 [33-77]	193 [21]	36 [12-73]	8.39
MF		192	36.5 [16.5-59.5]	3420 [409]	15 [5-28]	7.92
	+ OAH	144	48 [23-68]	2181 [284]	17 [8-37]	7.68
	+ OAH + other	64	61.5 [33.5-75]	914 [114]	26 [14-49]	8.02
	+ other (no OAH)	83	53 [26-68]	1158 [167]	26 [9-45]	6.93
	+ other INCS	7	33 [0-77]	113 [21]	20 [6-79]	5.38
FP		33	44 [30-65]	156 [55]	23.5 [3.5-52]	2.83
	+ OAH	34	56 [40-67]	305 [64]	19 [10-46]	4.77
	+ OAH + other	14	52.5 [45-80]	60 [21]	54 [24.5-82.5]	2.89
	+ other (no OAH)	13	41 [31-59]	121 [22]	22 [18-41]	5.50
	+ other INCS	3	4 [0-65]	127 [11]	22 [8-48]	11.55

***: monotherapy**

FF: Fluticasone Furoate, FP: Fluticasone Propionate, MF: Mometasone Furoate, AZeFlu: Azelastine-Fluticasone Propionate

p25: 25th percentile; p75: 75th percentile

703 **Table 3. Day 1 versus non-consecutive days**

	Day 1		1st non-consecutive day		Other non-consecutive day		P value*
	N	VAS global, median [p25-p75]	N	VAS global, median [p25-p75]	N	VAS global, median [p25-p75]	Day 1 vs 1st non-consecutive day
All days	4132	34 [12-60]	4132	25 [7-51]	24680	12 [2-32]	<0.001
No treatment	2214	26 [7-51]	2154	18 [4-44]	13651	8 [0-24]	<0.001
AzeFlu	162	44 [19-69]	187	26 [9-55]	1566	17 [6-35]	<0.001
Other INCS treatment	555	43 [22-64]	601	30 [11-55]	3403	17 [6-38]	<0.001

704 *Statistical analysis by Wilcoxon and Mann-Whitney test

705 p25: 25th percentile; p75: 75th percentile

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Figure 1. Flow-chart of the study population

Figure 2: Percentage of days in each category of INCS treatment (first day and full data set)

Figure 3: Percentage of days in each category of treatment for VAS global measured (full dataset)

Fig 1

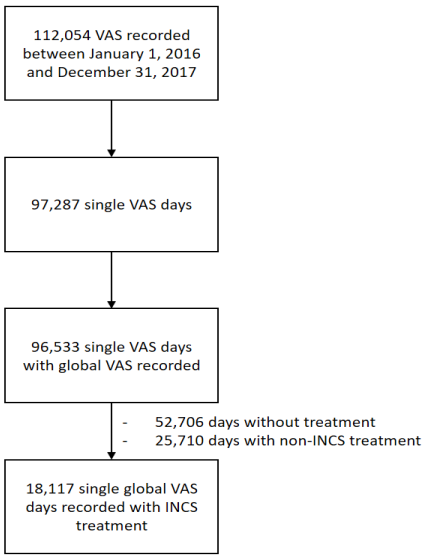
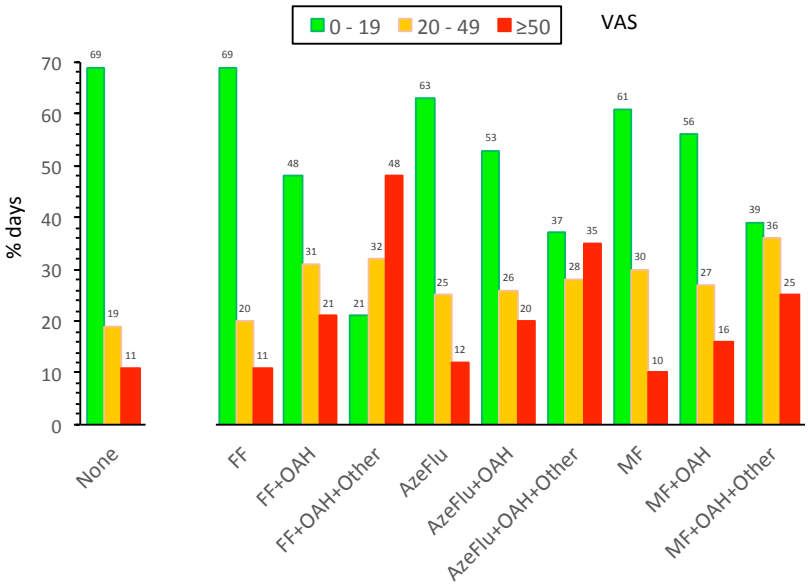

112,054 VAS recorded between January 1, 2016 and December 31, 2017
97,287 single VAS days
96,533 single VAS days with global VAS recorded
- 52,706 days without treatment
- 25,710 days with non-INCS treatment
18,117 single global VAS days recorded with INCS treatment

Fig 2


0 - 19
20 - 49
≥50
VAS
% days
70
60
50
40
30
20
10
0
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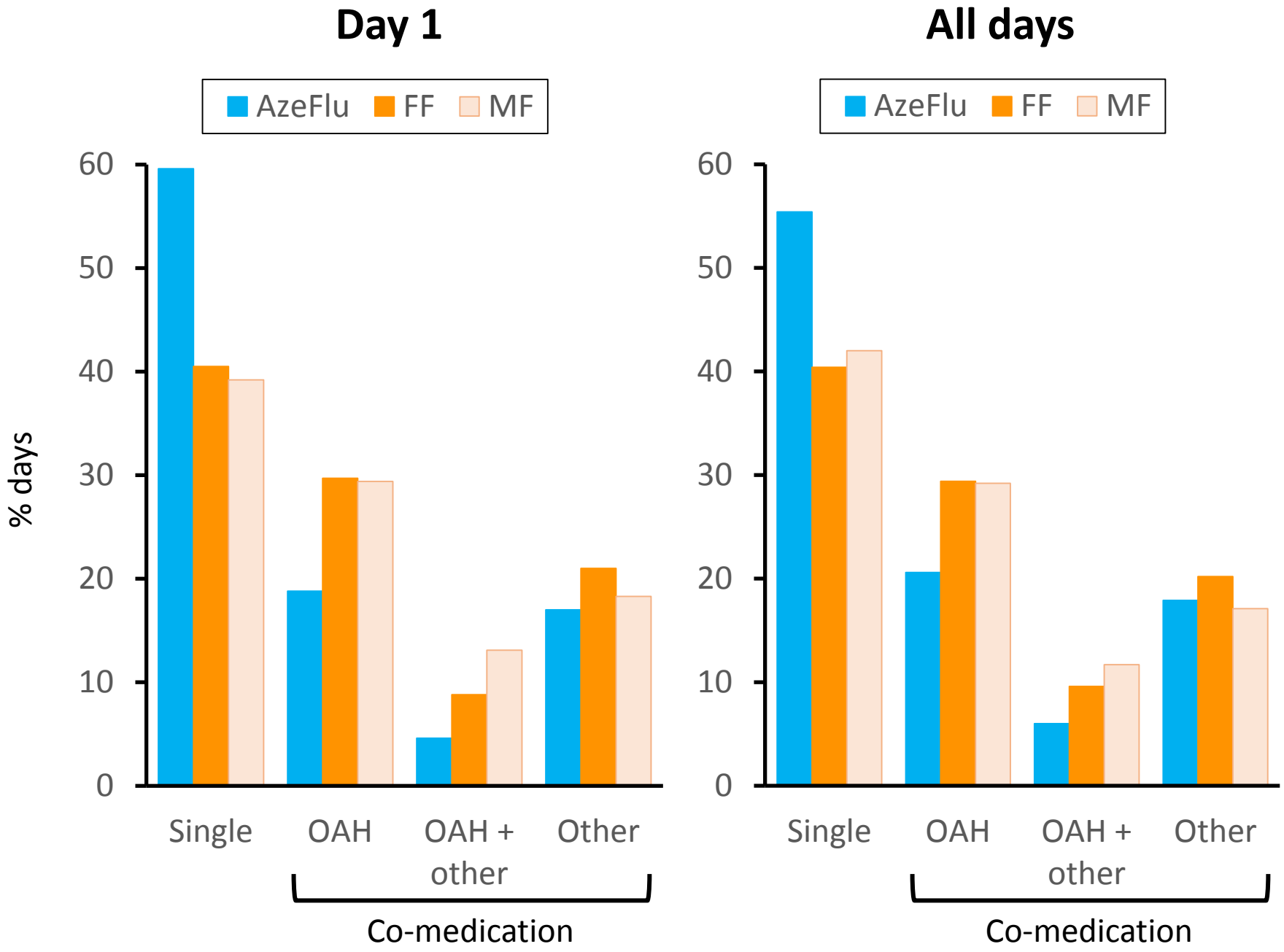
19
11
69
20
11
48
31
21
21
32
48
63
25
12
53
26
20
37
28
35
61
30
10
56
27
16
39
36
25
None
FF
FF+OAH
FF+OAH+Other
AzeFlu
AzeFlu+OAH
AzeFlu+OAH+Other
MF
MF+OAH
MF+OAH+Other


Day 1
All days
AzeFlu
FF
MF
% days
60
50
40
30
20
10
0
Single
OAH
OAH + other
Other
Co-medication