Review article

Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence

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The selection of pharmacotherapy for patients with allergic rhinitis aims to control the disease and depends on many factors. Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines have considerably improved the treatment of allergic rhinitis. However, there is an increasing trend toward use of real-world evidence to inform clinical practice, especially because randomized controlled trials are often limited with regard to the applicability of results. The Contre les Maladies Chroniques pour un Vieillissement Actif (MACVIA) algorithm has proposed an allergic rhinitis treatment by a consensus group. This simple algorithm can be used to step up or step down allergic rhinitis treatment. Next-generation guidelines for the pharmacologic treatment of allergic rhinitis were developed by using existing GRADE-based guidelines for the disease, real-world evidence provided by mobile technology, and additive studies (allergen chamber studies) to refine the MACVIA algorithm. (J Allergy Clin Immunol 2020;145:70-80.)

Key words: *Allergic rhinitis, Allergic Rhinitis and Its Impact on Asthma, Grading of Recommendations Assessment, Development and Evaluation, guidelines, real-world evidence*

Abbreviations used

ARIA:	Allergic Rhinitis and Its Impact on Asthma
GRADE:	Grading of Recommendations Assessment, Development and Evaluation
ICP:	Integrated care pathway
INCS:	Intranasal corticosteroid
MACVIA:	Contre les Maladies Chroniques pour un Vieillissement Actif
MASK:	Mobile Airways Sentinel Network
mHealth:	Mobile Health
MPAzeFlu:	Azelastine–fluticasone propionate combination
MPR:	Medication possession ratio
PDC:	Proportion of days covered
RWE:	Real-world evidence
VAS:	Visual analogue scale
WHO:	World Health Organization

Selection of pharmacotherapy for patients with allergic rhinitis aims to control the disease and depends on (1) patient empowerment, preferences, and age; (2) prominent symptoms, symptom severity, and multimorbidity; (3) efficacy and safety of treatment[1]; (4) speed of onset of action of treatment; (5) current treatment; (6) historic response to treatment; (7) effect on sleep and work productivity[2,3]; (8) self-management strategies; and (9) resource use.[4,5]

An algorithm was devised[5] and digitalized[6] to step up or step down allergic rhinitis treatment based on control. However, its

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use varies depending on the availability of medications and resources. Algorithms require testing with real-world evidence (RWE) that includes randomized controlled trials and observational research with real-world data.[7-9]

To evaluate estimates of effects, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology explicitly considers all types of study designs from randomized controlled trials to case reports, although guideline developers often restrict guidelines to randomized controlled trials.[10-12] GRADE also considers evidence on prognosis, diagnosis, values and preferences, acceptability, and feasibility or directness of findings. There is an increasing trend

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FIG 1. Organizations supporting the meeting (Paris; December 3, 2018). *CEmPac*, Centre for Empowering Patients and Communities; *EAACI*, European Academy of Allergy and Clinical Immunology; *EIT Health*, European Institute for Innovation and Technology; *EFA*, European Federation of Allergy and Airways Diseases Patients' Associations; *ERS*, European Respiratory Society; *Euforea*, European Forum for Research and Education in Allergy and Airways Diseases; *GA²LEN*, Global Allergy and Asthma European Network; *GARD*, Global Alliance against Chronic Respiratory Diseases (WHO Alliance); *GINA*, Global Initiative for Asthma; *POLLAR*, Impact of Air Pollution in Asthma and Rhinitis; *SFA*, Société française d'Allergologie; *SPLF*, Societé de Pneumologie de Langue Française; *WAO*, World Allergy Organization.

to use real-world data to inform clinical practice, especially because randomized controlled trials are often limited to the applicability of results.[13] The tradeoff that is made is one between risk of bias, primarily selection and confounding bias, and applicability. Ideally, both types of evidence are merged.

Guidelines are not sufficiently followed because they are not close enough to patients' needs and probably do not reflect real life. In cluster-randomized trials guideline-driven treatment is more effective than free treatment choice.[14,15] Moreover, guidelines (in rhinitis but also in asthma) have led to a better understanding of the treatment of the disease and have had an important teaching role that has led to change management.[16]

In addition, there is a need to support transformation of the health care system for integrated care with organizational health literacy.[16,17] During a recent meeting held in Paris (December 3, 2018) for chronic disease care, Mobile Airways Sentinel Network (MASK)[18] and Impact of Air Pollution on Asthma and Rhinitis (POLLAR; European Institute for Innovation and Technology–Health [EIT Health]),[19] in collaboration with professional and patient organizations in the field of allergy and airway diseases (Fig 1), recommended the evaluation of real-life care pathways (integrated care pathways [ICPs]) centered around the patient with rhinitis and asthma.

During the ICP meeting in Paris, next-generation guidelines for the pharmacologic treatment of allergic rhinitis were developed by using existing GRADE-based guidelines for allergic rhinitis,[5,20-22] RWE provided by randomized controlled trials, real-world data using mobile technology,[23,24] and chamber studies (Fig 2).[5,6,16-20,25-27] These recommendations were used to refine the algorithm for allergic rhinitis treatment proposed by a consensus group.[5]

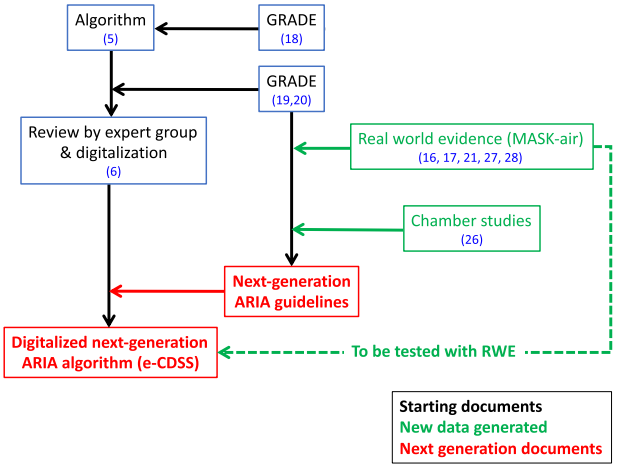

FIG 2. Development of next-generation ARIA guidelines.

The present report describes the process of next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA)–GRADE guidelines for the pharmacologic treatment of allergic rhinitis.

DOCUMENTS CONSIDERED FOR DEVELOPMENT OF ARIA CARE PATHWAYS

Contre les Maladies Chroniques pour un Vieillissement Actif (MACVIA) algorithm proposing a stepwise approach for allergic rhinitis pharmacologic treatment

An algorithm based on the visual analogue scale (VAS)[28] has been devised by the ARIA expert group (1) for selection of pharmacotherapy for patients with allergic rhinitis and (2) to

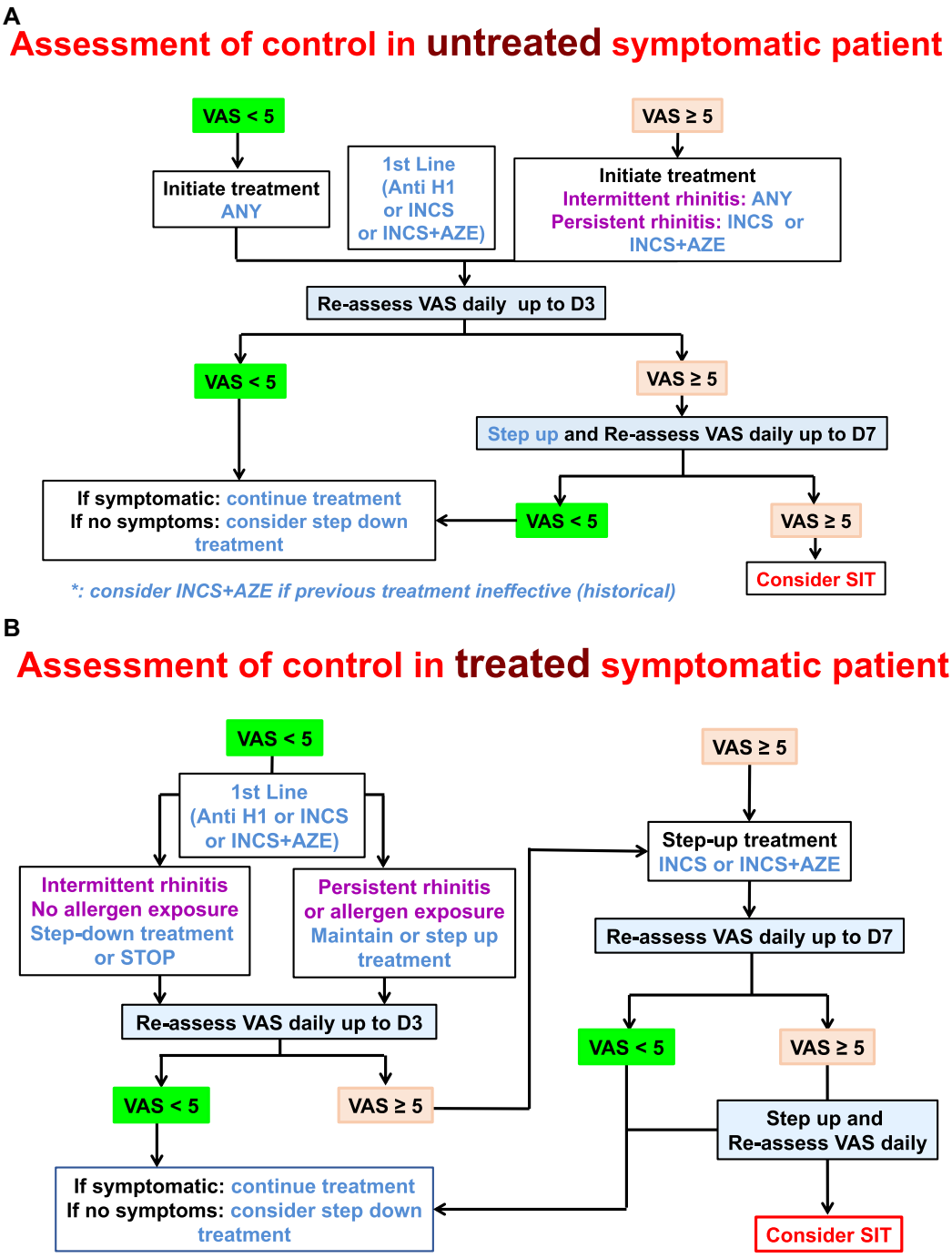

FIG 3. A, Step-up algorithm in untreated patients using VASs (adolescents and adults).[5] The proposed algorithm considers the treatment steps and the patient's preference. VAS levels are shown in ratios. If ocular symptoms remain once treatment has been initiated, add intraocular treatment. **B,** Step-up algorithm in treated patients using VASs (adolescents and adults).[5] The proposed algorithm considers the treatment steps and the patient's preference. VAS levels are shown in ratios. If remaining ocular symptoms, add intraocular treatment.

step up or step down treatment depending on control (Fig 3).[5] The ARIA algorithm for allergic rhinitis was revised by an expert group, and a proposal was made to classify allergic rhinitis treatments (Table I).[6]

ARIA 2010, 2016 revision, and US Practice Parameters 2017

Although few head-to-head comparisons of medications during randomized controlled trials are available,[29-32] the comparison of

TABLE I. Classification of treatments used in patients with allergic rhinitis[6]

T1	Nonsedating H_1-antihistamine (oral, intranasal, and ocular), leukotriene receptor antagonists, or cromones (intranasal and ocular)
T2	INCSs
T3	INCSs + intranasal azelastine
T4	Oral corticosteroid as a short course and an add-on treatment
T5	Consider referral to a specialist and allergen immunotherapy

allergic rhinitis medications has been proposed by several reviews[1] and guidelines.[5,20-22] A health technology assessment evaluation concluded that most allergic rhinitis medications had a similar effect.[33] However, this study used a method that did not enable differentiation between medications.

The ARIA revision 2016[21] and US Practice Parameters 2017[22] were developed independently and used the same methodological approach: GRADE.[10-12] Interestingly, the same questions were considered. Two major outcomes were considered in the treatment of moderate-to-severe rhinitis: efficacy and speed of action (Table II).[21,22]

Although the GRADE approach suggests the use of all relevant evidence, developers of recommendations have focused on randomized controlled trials.

ARIA 2016 revision[21] and US Practice Parameters 2017[22] mainly based on Randomized Control Trials support the MACVIA algorithm.[5]

Speed of onset of action of medications

The US Food and Drug Administration has proposed 3 study types to assess the onset of action of allergic rhinitis medications[25,34]: the standard phase III double-blind randomized controlled trial, park setting studies, and allergen exposure chamber studies.[35] Randomized controlled trials are informative but cannot provide sufficient precision to assess onset of efficacy because they cannot allow repeated timing over short periods of time (minutes). Allergen exposure chambers offer some advantages over randomized controlled trials in assessing the onset of action of medications that can be demonstrated in minutes.[35] The allergen exposure chamber allows consistent allergen exposure. However, it is a manipulated *in vivo* procedure, whereas the park study mirrors real-life exposure. Park studies have not captured both the early time and the allergen exposure chamber. It appears that a crossover trial would be difficult with a park study because of variations in allergen exposure between days. On the other hand, the allergen exposure chamber cannot replace real-world allergen exposure but can only complement it. Allergen exposure chamber studies appear more robust than park studies. To date, the allergen exposure chamber studies that have been conducted have been monocentric and have followed protocols unique to each center. Because there are technical differences in each allergen exposure chamber, it is not easy to compare the results obtained in the different allergen exposure chambers,[36] although standardization has begun for some of them.[37]

In the Ontario and Vienna allergen exposure chambers, several medications have been tested (Table III).[26,27,38-51]

TABLE II. Overall recommendations using GRADE

ARIA 2016[21]

1. In patients with SAR, we suggest either a combination of INCS + OAH or INCS alone, but the potential net benefit might not justify spending additional resources.
2. In patients with PAR, INCSs alone are recommended rather than a combination of an INCS + an OAH.
3. In patients with SAR, we suggest either a combination of an INCS + an INAH or an INCS alone, but the choice of treatment depends on patient preferences. At initiation of treatment (first 2 weeks), a combination of an INCS + an INAH might act faster than an INCS alone and might therefore be preferred by some patients. In settings in which the additional cost of combination therapy is not large, a combination therapy might be a reasonable choice.
4. In patients with PAR, we suggest either a combination of an INCS + an INAH or an INCS alone.

For all of these recommendations, the level of evidence was low[2,3] or very low.[1,4]

US practice parameters 2017[22]

For initial treatment of nasal symptoms of SAR in patients ≥12 years of age, clinicians:

- should routinely prescribe monotherapy with an INCS rather than a combination of an INCS and an oral H_1-antihistamine or
- should recommend an INCS over an LTRA (for ≥15 years of age).
- For moderate-to-severe symptoms, clinicians can recommend the combination of an INCS and an INAH.

INAH, Intranasal antihistamine; *LTRA*, leukotriene receptor antagonist; *OAH*, oral antihistamine; *PAR*, perennial allergic rhinitis; *SAR*, seasonal allergic rhinitis.

The Ontario chamber studies show the rapid onset of efficacy for azelastine and its combinations. There does not seem to be a difference between azelastine alone or in combination. Other intranasal H_1-antihistamines have a slower onset of action. Intranasal corticosteroids (INCSs; alone or with oral H_1-antihistamines) are not effective before 2 hours. The Vienna chamber studies show that azelastine and levocabastine/fluticasone furoate are the fastest-acting medications by comparison with oral H_1-antihistamines.

RWE using mobile technology

According to the World Health Organization (WHO), Mobile Health (mHealth) has the potential to transform health service delivery globally.[52] Next-generation ARIA guidelines should consider testing recommendations based on the GRADE approach with direct RWE by using data obtained by using mHealth tools to confirm or refine current GRADE-based recommendations.

Although many mHealth tools are available for the assessment of allergic rhinitis,[53] only MASK has reported data on medications that can be used in RWE. MASK, a new development of ARIA, is an information and communication technology system centered around the patient (adolescents and adults).[19,54] MASK, which is freely available in the Google Play and Apple Stores, can inform patient decisions on the basis of a self-care plan proposed by the health care professional.[18,19] It uses a treatment scroll list including all medications customized for each country, as well as VASs to assess rhinitis control and work productivity. MASK is deployed in 23 countries and 17 languages,[55] with more than 30,000 users. It was selected by the European Commission's Directorate-General for Health and Food Safety and by the newly established Commission Expert Group "Steering Group on Health Promotion, Disease Prevention

TABLE III. Comparison of the time of onset of action using environmental exposure chambers

Drug (dose)	Formulation	Onset of action	Parameter	Reference
Ontario environmental exposure chamber[38]				
Azelastine	Nasal spray	15 min	TNSS	38
MPAzeFlu	Nasal spray	5 min	TNSS	37
Fluticasone propionate + oral loratadine (10 mg)	Nasal spray + tablet	160 min		
Olopatadine	Nasal spray	90 min	TNSS	39
Ciclesonide	Nasal spray	60 min	TNSS	40
Budesonide	Nasal spray	8 h	TNSS	41
Budesonide and azelastine	Nasal spray	20 min		
CDX-313 (solubilized budesonide + azelastine)	Nasal spray	20 min		
Levocetirizine	Tablet	160 min	MSS	42
Vienna environmental exposure chamber				
Astemisole-D, Loratadine-D	Tablet	65-70 min	No placebo MSS	43
Astemisole, loratadine, terfenadine-forte	Tablet	107-153 min	No placebo MSS	44
Azelastine (intranasal), desloratadine	Nasal/tablet	Azelastine: 15 min Desloratadine: 150 min	TNSS	45
Bilastine, cetirizine, fexofenadine	Tablet	No assessment before 60 min	TNSS	46
Cetirizine-D, budesonide	Nasal/tablet		No placebo	47
Cetirizine-D, xylometazoline nasal spray	Nasal/tablet		No placebo	48
Desloratadine	Tablet	30 min	Obstruction	49
Fluticasone furoate and levocabastine	Nasal spray	Combi: 15 min No data for fluticasone furoate or levocabastine	TNSS	50
Levocetirizine, loratadine	Tablet	Levocetirizine: 45 min Loratadine: 60 min	MSS	51
Rupatadine	Tablet	15 min	TNSS	52

Aze, Azelastine hydrochloride; *MSS*, mixed symptom score; *TNSS*, total nasal symptom score.

TABLE IV. Information used to support next-generation ARIA-GRADE guidelines

	GRADE recommendation	mHealth RWE	Chamber studies
Oral H_1-antihistamines are less potent than INCSs BUT many patients prefer oral drugs	21 No information on patient's preference	24,25 No information on patient's preference	
Intranasal H_1-antihistamines are less effective than INCSs	21		
Intranasal H_1-antihistamines are effective within minutes	21		40, 46
INCSs should continue being prescribed as first-line therapy in patients with moderate-to-severe rhinitis	21, 23	24, 25	
Onset of action of INCSs takes a few hours to a few days (ciclesonide has a faster onset)	21		42, 43
The combination of INCSs and oral H_1-antihistamines offers no advantage over INCSs	22, 23	24, 25	
The combination of INCSs and intranasal H_1-antihistamines is more effective than INCSs	YES in patients with moderate-to-severe disease: 23 With restriction: 22	24, 25	
The combination of INCSs and intranasal H_1-antihistamines is effective within minutes			39, 43, 51
Leukotriene antagonists are less potent than INCSs	23		39, 43, 51

The studies are summarized in the Online Repository.

and Management of Non-Communicable Diseases" as a good practice that can be scaled up in the field of digitally enabled, integrated, person-centered care.[56]

Messages from MASK. Two studies in more than 9000 users and 22 countries[24,57] confirmed a pilot study[23] and allowed differentiation between allergic rhinitis treatments. They also showed that the assessment of days was useful in understanding treatment patterns. Their results combine to indicate that the following are true in real life:

1. Patients are poorly adherent to treatment.[23,57]
2. No treatment trajectory could be identified,[24] and most patients self-medicate.
3. Most patients with rhinitis use on-demand treatment when their symptoms are suboptimally controlled. When symptoms are uncontrolled, they change their medications daily for control.[23]
4. The vast majority of patients do not follow guidelines or physicians' prescriptions.[23,24,57]

TABLE V. Consensus opinion for the different scenarios[6]

	Part 1: Approach to treatment			
	Patient VAS	**Phenotype**	**Tx**	**Consensus**
1	≥5	IAR or PER	Yes	Step-up
2	≥2 to <5	IAR	Yes	Continue
3	<2	IAR	Yes	Step-down
4	≥2 to <5	PER	Yes	Continue or step-up
5	<2	PER	Yes	Step-down
6	≥5	IAR	No	Initiate
7	≥5	PER	No	Initiate
8	<5	IAR or PER	No	Initiate

	Part 2: Specific treatment step-ups		
	Current Tx	**Step-ups**	**Notes**
9	T1	T2 or T3	
10	T2	T3	
11	T3	T3 + T4*	Consider T5†
12	T1 + T2	T3	Consider T5†
13	T1 + T3	T3 + T4*	Consider T5†
14	T2 + T3	T3 + T4	Consider T5†
15	T5 + VAS ≥5	T5 + T>2 or T3	
16	T5 + VAS ≥2 to <5	T5 + T1, T2 or T3	T5 + T2 or T3 if congestion
17	T5 + T1	T5 + T2 or T3	
18	T5 + T2	T5 + T3	
19	T5 + T3	Continue	Consider referral

	Part 3: Specific treatment step-downs		
	Current Tx	**Step-down**	**Notes**
20	T3	T2 or T1	T2 if congestion
21	T2	T1	Continue T2 if congestion
22	T1	Stop	Not exposed to allergen
23	T1	Continue	Exposed to allergen
24	T1 + T2	T1 or T2	T2 if congestion
25	T1 + T3	T1 or T3	T3 if congestion
26	T2 + T3	T2 or T3	
27	T5 + T3	T5 + T1 or T2	T5 + T2 if congestion
28	T5 + T2	T5 + T1	Continue T5 + T2 if congestion
29	T5 + T1	T5	Not exposed to allergen
30	T5 + T1	T5 + T1	Exposed to allergen
31	T5	T5	Until end of course

	Part 4: Treatment initiation			
	Patients	**Tx**	**Consensus**	**Note**
32	IAR; VAS ≥5	No	T1, T2, or T3	T2 or T3 if congestion
33	PER; VAS ≥5	No	T2 or T3	
34	IAR or PER VAS <5	No	T1, T2, or T3	T2 or T3 if congestion

IAR, Intermittent allergic rhinitis; *PAR*, persistent allergic rhinitis; *T1*, antihistamine (oral, intranasal, or eyedrop), leukotriene receptor antagonist or cromones (intranasal or eyedrops); *T2*, INCS; *T4*, INCS + intranasal antihistamine; *T5*, consider referral and allergen immunotherapy; *Tx*, treatment.
*Short course (3-7 days).
†If VAS score remains ≥5/10.

5. When physicians are allergic, they behave like patients,[58] suggesting the need for behavioral science to improve control.
6. Patients who do not take medications usually have well-controlled symptoms.[23,24]
7. Patients reporting monotherapy with INCS-containing medications have a similar control level.[23,24] However, azelastine–fluticasone propionate combination (MPAze-Flu) is significantly more often administered as a single therapy than fluticasone furoate or mometasone furoate.
8. Patients reporting oral H_1-antihistamine monotherapy have a poorer level of control than those reporting INCS-containing medications.[23,24]
9. Most patients have a worse control level with increasing medications,[23,24] contradicting guidelines that propose to increase the treatment level to achieve control.
10. These results indicate that when patients' symptoms are controlled, either they do not take a medication or remain with a single treatment. When their symptoms are uncontrolled, they comedicate.

11. Considering control level and comedication, MPAzeFlu is more effective than INCSs.[23,24]
12. Resistant hypertension is defined by the number of medications used to control the disease,[59] and a similar classification might be proposed in patients with allergic rhinitis, confirming the severe chronic upper airway disease concept.[60]

Limitations of MASK. As for all studies using participatory data, potential biases include (1) the likelihood of sampling bias, which makes it difficult to assess the generalizability of the study; (2) outcome misclassification that cannot be assessed; and (3) because of ethical considerations, availability of very little information on patient (or day) characteristics. App users are not representative of all patients with rhinitis.

MASK studies have used days in cross-sectional analyses[18,19] because there is no clear pattern for a defined treatment, and a longitudinal study was not feasible because users mostly use the app intermittently.

The diagnosis of allergic rhinitis was not supported by a physician but was a response to the following question: "Do you have allergic rhinitis? Yes/no." Therefore some users with no rhinitis might have responded "yes" to the question, but more than 95% of responders declared symptoms of rhinitis by questionnaire. There are potential measurement biases when using apps, including collection of information, education of the patient, age, availability, and ability to use a smartphone.[23] Precise patient characterization is impossible using an app, but every observational study using MASK has been able to identify days with poor control or criteria of severity.[61-65]

Adherence to treatment is impossible to obtain directly because patients do not report data every day and might not report all medications used. Electronic counters on delivery devices could be used to obtain more complete data on adherence.

Nonetheless, mobile technology is becoming an important tool for better understanding and managing allergic rhinitis. It adds novel information that was not available with other methods.[61-67] In addition, the mere number of observations that mobile technology can provide offers an unprecedented body of evidence that can complement conventional randomized controlled trials for RWE.

Other RWE studies using mobile technology. To our knowledge, no other mHealth study has assessed the efficacy of different medications on a large scale.

Physician's perspectives

There is a complete disconnection between the physician's prescriptions and the patient's behavior for the treatment of pollen-induced allergic rhinitis. The vast majority of allergists prescribe medications for the entire season, recommending the patient to use them regularly, even during days with few symptoms. Some allergists prescribe a preseason treatment without clear evidence of efficacy. On the other hand, the vast majority of patients use their medications on demand when their allergic rhinitis is not well controlled and they do not follow guidelines.[18,19]

When physicians are patients themselves, they behave like patients when they treat their own allergic rhinitis and do not follow the prescriptions, as recently reported.[58] Health literacy is an important component of adherence to medications,[68,69] but given the behavior of allergists as patients, it appears that other factors are more important. Possibly, it is human nature that drives adherence to treatment irrespective of whether the patient is a physician, and behavioral science is an important need to be considered in medical care.

Lack of adherence is very common in allergists with allergic rhinitis and prescribed long-term treatment.

NEXT-GENERATION ARIA-GRADE GUIDELINES

Recommendations have been refined with RWE and chamber studies (Table IV).[20-24,38,39,41,42,45,50] The algorithm proposed in Fig 3 is also supported by the present data.

The approach proposed in this article confirms most GRADE recommendations for allergic rhinitis and the classification of allergic rhinitis treatments proposed by ARIA (Table I).[6] Some conditional evidence was supported by RWE:

- The combination of oral H_1-antihistamines with INCSs was not found to be more effective than INCSs alone.
- The combination of intranasal H_1-antihistamines with INCSs was found to be more effective than INCSs alone.
- Intranasal H_1-antihistamine–containing medications are effective within minutes.

NEXT-GENERATION ARIA ALGORITHM

The overall ARIA algorithm[5] was found to be appropriate, and no change is needed. The step-up and step-down approach proposed by ARIA experts[6] based on the ARIA algorithm has been confirmed (Table V). However, the different steps need further validation with RWE.

CONCLUSIONS

In this report we present the first GRADE-based guideline integrating RWE and supportive studies (chamber studies) in the management of allergic rhinitis. This approach could be considered a model for chronic diseases.

These guidelines will inform ICPs and will be included in the European Commission's Directorate-General for Health and Food Safety digitally-enabled, integrated, person-centered care.[70] They will represent the change management strategy of ARIA, phase 4.[16]

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SUPPLEMENTARY DATA

Although many mHealth tools are available for the assessment of AR,[E1] only MASK has reported data on medications that can be used in RWE. MASK, a new development of ARIA, is an information and communication technology system centered around the patient in adolescents and adults.[E2,E3] MASK, which is freely available in the Google Play and Apple stores, can inform patient decisions on the basis of a self-care plan proposed by the health care professional.[E2,E4-E11] It uses a treatment scroll list including all medications customized for each country and a VAS to assess rhinitis control and work productivity. MASK is deployed in 23 countries and 17 languages,[E12] with more than 26,000 users. It was selected by the European Commission's Directorate-General for Health and Food Safety and the newly established Commission Expert Group "Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases" as a good practice in the field of digitally enabled, integrated, person-centered care.[E13]

2016 MASK treatment study[E7]

Background. A pilot study attempted to provide additional and complementary insights into real-life treatment of allergic rhinitis using MASK.

Methods. MASK collected daily VAS scores for overall allergic symptoms (VAS global) in 15 countries. Because of privacy concerns, MASK, as any other mobile technology, cannot assess the characteristics of the patient.

Results. Two thousand eight hundred seventy-one users filled in 17,091 days of VASs between June 1, 2015, and May 30, 2016. Medications were reported for 9,634 days.

- Patients did not follow guidelines and often self-medicated.
- Adherence to treatment was poor.
- MASK allowed differentiation between treatments within or between classes (INCS containing medications and oral H_1-antihistamines). Untreated days (days reported without any treatment) had the best control. Days with reported INCSs or MPAzeFlu had similar control. Days with cetirizine alone had worse control. Days with loratadine alone or any cotherapy had the worst control.
- Users reporting intranasal MPAzeFlu used comedication on 30% to 35% of days, whereas those reporting INCSs used comedication on 45% to 60% of days.
- Very few users reported oral corticosteroids, and VAS levels were usually high.
- This RWE study brings new information on the treatment of patients with AR, suggesting the following: First, patients treat themselves as needed depending on disease control and increase their treatment when they are unwell. However, comedication does not improve the median control. Second, MPAzeFlu is superior to INCSs because, when symptoms are controlled, patients do not comedicate, and comedication is more common in those who used INCSs.

The MASK 2016 study indicated low adherence and allowed comparative efficacy of medications by using a novel approach.

2017 MASK treatment study[E14]

Objectives. A cross-sectional real-world observational study was undertaken in 22 countries to complement the 2017 pilot study.[E7]

Methods. MASK was used to collect data of daily VAS scores for (1) overall allergic symptoms; (2) nasal, ocular, and asthma symptoms; and (3) work, as well as medication use. The 3 most common intranasal medications containing INCSs (fluticasone furoate, mometasone furoate, and fluticasone propionate), MPAzeFlu, and 8 oral H_1-antihistamines were studied. The study included some of the users of the pilot study (to achieve a sufficient number of users per drug), [E7] but outcomes differed.

Results. Nine thousand one hundred twenty-two users filled in 112,054 days of VASs in 2016 and 2017 (Fig E1).

- As shown in the pilot study,[E7] similar control levels were found for single treatment with INCSs or MPAzeFlu (good control), but more users needed INCSs to be combined with another treatment (worst control) compared with MPAzeFlu.
- INCSs or MPAzeFlu resulted in more control days than oral H_1-antihistamines.
- The same trend was found for VAS scores for asthma, eye symptoms, and work productivity.

The 2017 MASK treatment study confirms MASK's usefulness in assessing behavior in patients with allergic rhinitis. A ranking of medications was possible and confirmed the MASK 2016 study. The 2 MASK treatment studies indicated that MPAzeFlu is the most effective and oral H_1-antihistamines are the least effective category of medication.

2018 MASK adherence study[E15]

Background. Mobile technology might help better understand adherence to treatment.

Objectives. We sought to assess adherence to treatment in patients with allergic rhinitis using the MASK app.

Methods. An observational cross-sectional study was carried out on all consecutive users who filled in MASK from January 1, 2016, to August 1, 2017. Secondary adherence was assessed by using modified medication possession ratio (MPR) and proportion of days covered (PDC is a newer and more conservative measure of refill record–based adherence).

- Proportion of MPR (modified MPR): ratio of days of medication use was reported to be used on days in a given time interval.
- PDC over a time interval (modified PDC): ratio of days of medication was reported to be used on days in the time interval between the first and the last record considered.

Results. Twelve thousand one hundred forty-three users were registered, and 6949 users had at least 1 VAS recording. Among them, 1887 (15.7%) users had 7 or more days of reporting VAS scores. One hundred thirty-six (11.28%) of them were adherent (MPR $\geq$ 70% and PDC $\leq$ 1.25).

The 2018 MASK adherence study indicated that adherence to treatment was estimated to be less than 5%.

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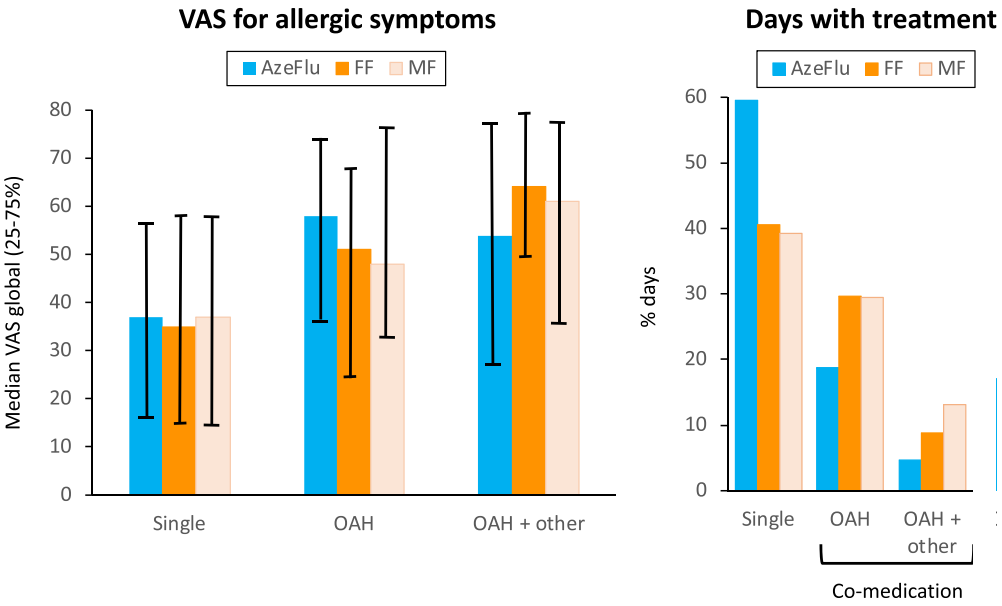

FIG E1. Efficacy of INCS-containing medications (VAS global) and percentage of days with comedications. *FF*, Fluticasone furoate; *MF*, mometasone furoate; *OAH*, oral H_1-antihistamine; *Other*, any other medication; *Single*, no comedication.