Allergic Rhinitis and its Impact on Asthma (ARIA)

Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs

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Allergic rhinitis (AR) and asthma represent global health problems for all age groups. Asthma and rhinitis frequently coexist in the same subjects. Allergic Rhinitis and its Impact on Asthma (ARIA) was initiated during a World Health Organization workshop in 1999 (published in 2001). ARIA has reclassified AR as mild/moderate-severe and intermittent/persistent. This classification closely reflects patients' needs and underlines the close relationship between rhinitis and asthma. Patients, clinicians, and other health care professionals are confronted with various treatment choices for the management of AR. This contributes to considerable variation in clinical practice, and worldwide, patients, clinicians, and other health care professionals are faced with uncertainty about the relative merits and downsides of the various treatment options. In its 2010 Revision, ARIA developed clinical practice guidelines for the management of AR and asthma comorbidities based on the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system. ARIA is disseminated and implemented in more than 50 countries of the world. Ten years after the publication of the ARIA World Health Organization workshop report, it is important to make a summary of its achievements and identify the still unmet clinical, research, and implementation needs to strengthen the 2011 European Union Priority on allergy and asthma in children. (J Allergy Clin Immunol 2012;130:1049-62.)

Key words: *Rhinitis, asthma, Allergic Rhinitis and its Impact on Asthma, allergy, GRADE*

Allergic rhinitis (AR) and asthma frequently coexist in the same subjects and represent a global health problem. Patients, clinicians, and other health care professionals worldwide are faced with the relative merits and downsides of the various treatment options. Clinical practice guidelines for AR management developed over the past 15 years[1,2] have improved the care of patients with AR.[3]

The outcomes of an expert workshop held at the World Health Organization (WHO) in December 1999 (Allergic Rhinitis and its Impact on Asthma [ARIA]) were published in 2001.[4] The ARIA workshop report was innovative in

- proposing a new AR classification using persistence and severity of symptoms;
- promoting the concept of comorbidities in asthma and rhinitis as a key factor for patients' management;
- developing guidelines in collaboration with all stakeholders, including primary care physicians and patients;
- including experts from developed and developing countries;
- adopting an evidence-based approach for the first time in guidelines on rhinitis[5]; and
- initiating global implementation among health care professionals and patients.

Finally, the International Primary Care Respiratory Group guidelines on AR were based on the ARIA workshop report.[6,7]

Guidelines must be updated. The ARIA update was published in 2008[8] by using the same evidence-based model.[5] This was a continuous process preceded by a literature review of the aspects not previously covered (eg, complementary and alternative medicine[9] and sports[10]), the update on the links between rhinitis and asthma,[11] and prevention[12] and treatment.[13,14]

Abbreviations used
AR: Allergic rhinitis
ARIA: Allergic Rhinitis and its Impact on Asthma
GRADE: Grading of Recommendation, Assessment, Development and Evaluation
RCT: Randomized controlled trial
WHO: World Health Organization

However, the transparent reporting of guidelines is needed to facilitate understanding and acceptance. ARIA was the first chronic respiratory disease guideline to adopt the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system, an advanced evidence evaluation methodology. The ARIA revision was published in 2010.[15]

Ten years after publication of the ARIA WHO workshop report, it is important to make a summary of its achievements and identify the still unmet clinical and research needs.

SCIENTIFIC PUBLICATIONS USING THE ARIA CLASSIFICATION

A Medline search carried out August 1, 2011, retrieved 251 original articles conducted in 43 countries that used the ARIA classification of intermittent and persistent AR. These studies have involved more than 170,000 subjects (see Table E1 in this article's Online Repository at www.jacionline.org), including preschool children, but no study has specifically targeted the elderly. The articles included epidemiologic studies in the general population (cross-sectional[16-23] and cohort[24]), observational studies among primary care physicians and specialists, and interventional studies, including 5 large-scale, double-blind, placebo-controlled trials.[25-29] Three Cochrane Collaboration reviews using the ARIA classification have been finalized,[30-32] and others are pending.

THE ARIA CLASSIFICATION OF AR IS CLOSE TO PATIENTS' NEEDS

The classification of AR was revised by ARIA in 2001. A major change was the introduction of the terms "intermittent" and "persistent."[4] Previously, AR was classified based on the time and type of exposure and symptoms as seasonal, perennial, and occupational.[2,33] However, this classification is not entirely satisfactory because of the following:

- In certain areas, pollens and molds are perennial allergens,[34] whereas house dust mites show seasonal trends.[35]
- Most patients are polysensitized to several different allergens and exposed throughout the year.[17,18,36,37]
- In the general population, a large number of patients with house dust mite allergy have intermittent rhinitis.[17,18,35]
- Because of the priming effect on the nasal mucosa induced by low levels of pollen allergens[38] and nasal minimal persistent inflammation in patients with symptom-free rhinitis,[39] symptoms do not necessarily occur strictly in conjunction with the allergen season.
- The ARIA classification appears to be closer to the patient's needs than the previous one.[17,40]

- An important argument for the use of "intermittent" and "persistent" is the need to harmonize AR with asthma, representing manifestations of the same condition in 2 parts of the airways.[41]

The phenotypes of seasonal and perennial rhinitis cannot be used interchangeably with the ARIA classification because they do not represent the same stratum of disease. Thus "intermittent" and "persistent" are not synonymous with "seasonal" and "perennial."[18,20,21,36,42] In 2008, the US rhinitis practice parameters[43] proposed the term "episodic" AR. This term has not been validated, although it might refer to intermittent AR.

COMORBIDITY BETWEEN ASTHMA AND RHINITIS

The links between rhinitis and asthma were identified 2 centuries ago. However, before the ARIA workshop, asthma and rhinitis comorbidity was disregarded, and even in 2012, some guidelines do not report these links properly. However, the ARIA update literature review clearly supported the links between the upper and the lower airways.[11] Most patients with asthma (both allergic and nonallergic) also have rhinitis, whereas 10% to 40% of patients with AR have asthma comorbidity.[11] Some,[36] but not all,[44] studies suggest that asthma is more common in patients with moderate-to-severe persistent rhinitis than in those with the other types of rhinitis. Strong interactions exist between asthma and rhinitis because of occupational environments.[45]

Large studies have found a link between the severity and/or control of both diseases in children and adults.[46-49] Moreover, patients with severe uncontrolled asthma commonly have severe nasal disease (often chronic rhinosinusitis).[50,51]

Rhinitis is not usually the first symptom to occur in preschool children during the atopic march.[52] However, rhinitis in subjects without asthma is a risk factor for asthma both in adults[53] and children.[54] In adulthood, the development of asthma in patients with rhinitis is often independent of allergy,[55] whereas in childhood, it is frequently associated with allergy.[54]

CLINICAL EFFECT OF THE ARIA CLASSIFICATION

Large observational cross-sectional studies have found that severity (mild-moderate to severe) and persistence (intermittent/persistent) are 2 separate and possibly independent components of rhinitis.

In studies often carried out in primary care settings, adults or children with moderate-to-severe rhinitis have a similar impairment of quality of life or productivity irrespective of whether they have intermittent or persistent rhinitis. Mean Rhinoconjunctivitis Quality of Life Questionnaires or visual analog scale scores are consistently higher in patients with moderate-to-severe rhinitis than in patients with mild rhinitis.[56-60]

SUBPHENOTYPING OF PATIENTS WITH AR

Severity is one of the phenotypic characteristics of allergic disease that has received particular attention. Severity fluctuates from year to year in relation to allergen exposure. Most patients seeking medical care present with moderate-to-severe AR,[56-60] whereas in the general population they have mild AR.[18] Severe chronic upper airway disease, as proposed by a joint ARIA–Global Allergy and Asthma European Network (GA^{2}LEN)–World Allergy Organization expert group,[61] is defined by patients whose symptoms are inadequately controlled despite adequate (ie, effective, safe, and acceptable) pharmacologic treatment based on guidelines. These patients have an impaired quality of life, affecting social functioning, sleep, and school/work performance.[62] This concept of a patient-oriented definition of severity has now been extended to all allergic diseases by a Mechanisms of the Development of Allergy (MeDALL)–GA^{2}LEN-ARIA expert group.[63]

Phenotyping subtypes might characterize and predict disease severity, progression, and response to treatment and might help identify unique targets for treatment. Heterogeneity also exists within each dimension of the disease (eg, eosinophils and asthma severity),[64] across diseases (eg, eosinophils in asthma), and in relation to comorbidities.[65] Phenotypes can change over time, possibly driven by allergic, infectious, or other triggers (PreDicta, http://www.predicta.eu).

ARIA STATEMENTS, POSITION PAPERS, AND RECOMMENDATIONS

The ARIA expert panel has produced several recommendations, statements, and position papers, often in collaboration with other organizations and/or the WHO Collaborating Center for Asthma and Rhinitis (Montpellier) (Table I).[61,66-69]

ARIA has proposed stepwise guidelines (Fig 1).[8]

ARIA 2010 REVISION

The ARIA 2010 Revision was developed following the GRADE approach[70] by the ARIA-GA^{2}LEN guideline panel[71] in total independence from the private sector.[15] It summarized the potential benefits and harms underlying the recommendations, as well as assumptions around the values and preferences that influenced the strength and direction of the recommendations.

Two independent methodologists developed evidence summaries with the help of an information scientist with experience in GRADE and 2 biostatisticians. Eight experienced clinician members of the ARIA executive committee completed the panel.

Formulating the recommendations included consideration of the quality of evidence, desirable and undesirable consequences of following the recommended course of action, and values and preferences of those for whom the recommendations are intended. For most of the recommendations, resource use (cost) was also taken into account.

Eighty health care practitioners (allergists; pediatricians; internal medicine; ear, nose, and throat or pulmonary specialists; primary care physicians; nurses; and pharmacists) and patients from more than 50 countries were consulted. As a result of input received, additional bibliographic searches were performed for more recent studies for 31 questions, and a newer consultation was carried out to finalize the ARIA revision.

Taking into account both adults and children, a total of 59 recommendations were proposed: 11 for prevention, 31 for pharmacotherapy, 11 for allergen-specific immunotherapy, 5 for complementary and alternative medicine, and 1 for a biologic (omalizumab, Table II).[15]

ARIA should be considered as a general guide, and physicians need to tailor these general recommendations to individual patients given that patients live in different environments and each one has a different genetic makeup, responding differently to allergens and medications.

The review of the literature identified many areas with few studies or only studies with a high risk of bias (Table II).[15] Many areas were identified requiring more rigorous systematic reviews or updating of existing systematic reviews.

Real-life studies are needed to confirm that the applicability of evidence obtained in randomized controlled trials (RCTs) translates into daily practice settings.[72] Pragmatic randomized trials have found that the guideline-based management of AR is more effective than free treatment choice.[56]

Nonetheless, the ARIA guideline panel believes that the recommendations reflect the best current treatment of patients with AR.[15]

Studies need to be conducted in special populations, including young children, elderly patients, patients with occupational AR and asthma, and patients in low-resource countries.

After the publication of the ARIA revision, certain comments by experts were published.[73,74] It was not considered that these comments should alter the conclusions published but rather that they should enhance the transparency of the discussion around the evidence.[75]

DISSEMINATION AND IMPLEMENTATION

Guidelines need simplicity and educational outputs (ie, Web-based activities [www.whiar.org, www.ariaenespanol.org],[76] pocket guides, and questionnaires[77]), which are essential to facilitate implementation.[78] The pocket guide, developed after the ARIA Workshop report, has been translated into more than 50 languages. A version for the pharmacist has also been produced.[79]

The 2008 update executive summary has been translated into more than 30 languages.[80-88] In the United States, a group proposed the adaptation of ARIA.[89]

All stakeholders, including specialists, primary care physicians, health care professionals, patients, the public, and the media, should be encouraged to use the guidelines and should be involved in the production of guideline summaries and educational materials.

In many countries, ARIA guidelines are known by primary care physicians and specialists.[90,91]

GLOBAL APPLICABILITY OF ARIA AND UNMET NEEDS

Many unmet needs for AR have been published. In this document, unmet needs specific to ARIA are proposed from existing ARIA documents.

1. AR phenotypes

- AR is strictly related to an immune-mediated mechanism, and for inhalant allergy, it is restricted to an IgE-mediated mechanism. However, nonallergic mechanisms can be intertwined with allergic ones.
- Subphenotyping of AR: Applying (partly) unsupervised statistical methods (eg, cluster analysis or factor analyses) to a population will enable the definition of phenotypic characteristics.
- Control of disease: Control and severity are not well delineated in patients with rhinitis. Severe chronic upper airway disease has defined patients with uncontrolled AR.[61] Measures of AR control include symptom scores, visual analog scale scores,[58] quality-of-life scores,[8,92] or scores with several items.[93,94] Research should identify the most appropriate AR control test that can be applied globally and in all settings.
- AR and asthma: Links between AR and asthma are well known, but unsupervised statistical methods need to be used to have a more objective view of the links.
- Pediatrics: ARIA documents have always considered pediatric issues. However, AR is very often overlooked and underdiagnosed, especially in preschool children.
- Elderly: Many patients with AR are older than 65 years. The presentation of the disease as well as the efficacy and safety of treatments can differ in older adults, but no data are available. Moreover, the effect of comorbidities on AR management is unclear.
- Personalized medicine: The main challenge for allergic diseases in the 21st century is to understand their complexity. The vast majority of patients with AR can be treated with a simple algorithm, but a substantial number have uncontrolled symptoms during treatment[62] and require a personalized (tailored) approach.

2. Management of AR

- Update of the ARIA revision: Guidelines need to be continuously updated with new published data and even new treatments (eg, intranasal combination of H_1-antihistamine and corticosteroid[95] or intranasal corticosteroids with an hydrofluoroalkane propellant).
- ARIA in primary care: Most patients with AR are seen in primary care, and guidelines should be adapted for this setting.[96-99] The adaptation of the ARIA 2010 Revision is ongoing in collaboration with the International Primary Care Respiratory Group.
- Comparison of ARIA and other guidelines: Guidelines for the management of AR differ somewhat because of the classification of AR but also due to the recommendations concerning treatment. It is of importance to compare the different options and assess why these differences exist.
- Pharmacists and other health care practitioners: The majority of AR medications are over the counter in most countries, but some over-the-counter drugs contain sedative oral H_1-antihistamines. It is important for pharmacists to advise patients. Management of the allergic child at school is also important.[100]

3. Patient empowerment

Asthma and AR should be appropriately diagnosed and controlled to satisfy patients' expectations. Patients need to be involved in their own care; this can be achieved through patient education and self-management plans. Patient organizations have been involved in the design, dissemination, and implementation of ARIA.

4. Clinical trials

In RCTs, it is essential to have clarity with regard to definitions of disease, severity, and control, as well as comorbidities and risk factors (eg, smoking). RCT outcomes should be validated and standardized, so that meaningful comparisons between RCTs can be made.[92]

TABLE I. ARIA statements, position papers, and recommendations

- European Academy of Allergy and Clinical Immunology: "Requirements for medications commonly used in AR treatment."[66]
- GA^{2}LEN–World Allergy Organization: "Unmet needs in severe chronic upper airway disease (SCUAD)."[61]
- GA^{2}LEN-WHO Collaborating Center: "Uniform definition of asthma severity, control, and exacerbations: document presented for the WHO Consultation on Severe Asthma."[67]
- GA^{2}LEN–WHO Collaborating Center: "Practical guide for skin prick tests in allergy to aeroallergens."[68]
- Mechanisms of the Development of Allergy (MeDALL)–GA^{2}LEN–WHO Collaborating Center: Severe chronic allergic (and related) diseases: a uniform approach (accepted for publication).
- GA^{2}LEN: "How to design and evaluate RCTs in immunotherapy for allergic rhinitis."[69]

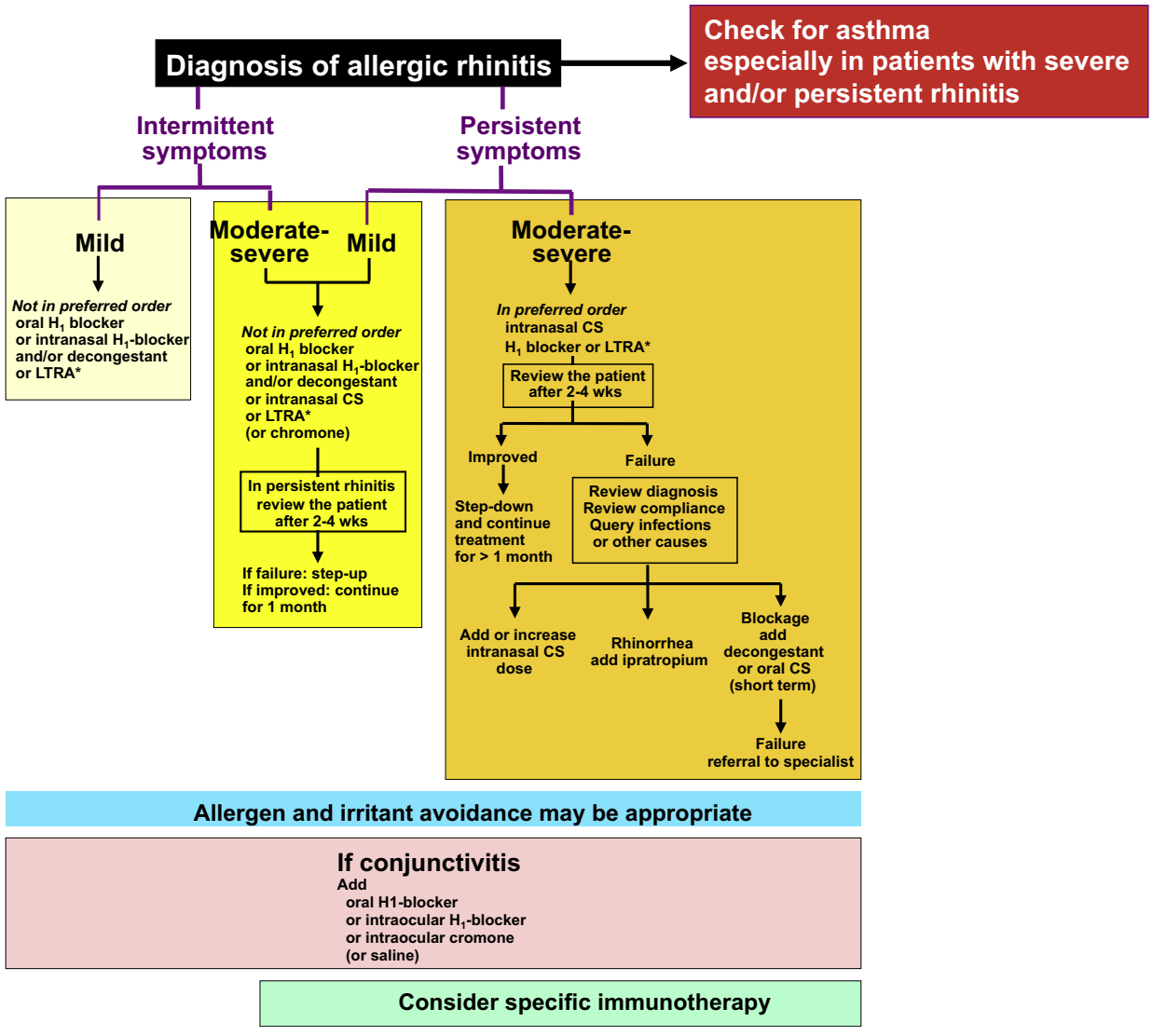

FIG 1. Recommendations of the ARIA update (from Bousquet et al[8]). *CS*, Corticosteroid; *LTRA*, leukotriene receptor antagonist.

5. Developing countries

A uniform definition of AR is applicable to the local and geographic conditions of all countries, phenotypes, and risk factors. ARIA implementation in developing countries should increase the availability and affordability of effective medications.

6. Research

Further research into severe allergic diseases is urgently needed to better understand the diseases and to provide novel therapeutic approaches. Global partnerships and platforms should ensure the application of standard methodology and protocols in the collection and sharing of samples and data.[67]

7. Epidemiology

In epidemiology, standardized definitions are fundamental for research, for the understanding of risk factors, and to enable comparisons across studies in different populations.

TABLE II. ARIA revision (from Brozek et al[15])

	Prevention of rhinitis or asthma	Management of rhinitis	Management of rhinitis and comorbid asthma
No. of clinical questions analyzed			
Total	11	39	9
Children	7	11	2
Adults	2	10	2
Not stated*	3	18	5
Quality of supporting evidence			
High	0	4	1
Moderate	0	8	3
Low	5	11	2
Very low	6	16	2
Recommendation			
High	3	6	1
Low	8	33	7

*Recommendation usually applicable to children and adults.

Mechanisms of the Development of Allergy (MeDALL) has developed a standardized AR definition for children (http://www.medall-fp7.eu).

8. Public health planning

In public health, a uniform definition of AR and severity is needed to identify prevalence, burden, and costs; to improve quality of care; and to optimize health care planning and policies.

9. Update of the ARIA revision

A conscientious analysis of the available evidence allows us to conclude that the absence of moderate or high quality points toward research gaps, particularly if it results in weak/conditional recommendations. In the face of strong recommendations, the research gaps are less likely to influence action.

10. Open access to ARIA membership

ARIA is open to all stakeholders globally, and requests for membership should be addressed to the WHO Collaborating Center for Asthma and Rhinitis (anna.bedbrook@inserm.fr).

INTERACTIONS WITH THE PRIVATE SECTOR

The private sector has been involved in ARIA with the status of observer, as described according to the WHO Global Alliance Against Chronic Respiratory Diseases (GARD) (http://www.who.int/gard):

- industry associations/umbrella organizations representing manufacturers of diagnostic reagents, devices, drugs, or other products or services relevant to the surveillance, prevention, and control of allergic and respiratory diseases and
- commercial enterprises and private sector entities.

The role of "observer" is also based on WHO Global Alliance Against Chronic Respiratory Diseases (GARD) (http://www.who.int/gard):

- There are no rights in the decision-making process, particularly in guideline development.
- Observers can make statements to present their views or positions on a specific issue only on invitation of the chairman (after agreement with the executive committee).
- The private sector is associated to the implementation and dissemination of ARIA.

ARIA IN THE POLITICAL AGENDA

ARIA was initiated during a WHO workshop (1999) and published in collaboration with WHO. It was then involved in the activities of the WHO Collaborating Center for Asthma and Rhinitis (Montpellier). The 2008 Update was carried out in collaboration with WHO, GA^{2}LEN (Framework Programme 6), and AllerGen (the Canadian network on allergy).

The European Medical Agency has accepted the ARIA classification of intermittent and persistent rhinitis.

ARIA has been used in several guidelines recommended by governmental health agencies (eg, Brazil, Portugal, Singapore, and the Finnish Allergy Plan[101]) or scientific societies. In certain countries, Health Technology Assessment is being started by using the ARIA 2010 Revision in collaboration with the Canadian Society for International Health.

The leading priority for the 2011 Polish Presidency of the Council of the European Union is to reduce health inequalities across European societies and, within its framework, to improve prevention and control of respiratory diseases in children.[102,103] ARIA research will strengthen the conclusions of the priority to reduce the burden of allergy and asthma in children for an improved active and healthy aging.

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