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


Rostrum

For a list of the authors' institutional affiliations and the disclosures of potential conflicts of interest, see Appendix 1.

Received for publication March 23, 2012; revised July 24, 2012; accepted for publication July 27, 2012.

Available online October 9, 2012.

Corresponding author: J. Bousquet, MD. Centre Hospitalier Universitaire, Montpellier, 34295-Montpellier-Cedex 05, France. E-mail: jean.bousquet@inserm.fr.

0091-6749/$36.00

© 2012 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2012.07.053
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, 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 have improved the care of patients with AR.

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

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.

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 and cohort), observational studies among primary care physicians and specialists, and interventional studies, including 5 large-scale, double-blind, placebo-controlled trials. Three Cochrane Collaboration reviews using the ARIA classification have been finalized, 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.” Previously, AR was classified based on the time and type of exposure and symptoms as seasonal, perennial, and occupational. However, this classification is not entirely satisfactory because of the following:

- In certain areas, pollens and molds are perennial allergens, whereas house dust mites show seasonal trends.
- Most patients are polysensitized to several different allergens and exposed throughout the year.
- In the general population, a large number of patients with house dust mite allergy have intermittent rhinitis.
- Because of the priming effect on the nasal mucosa induced by low levels of pollen allergens and nasal minimal persistent inflammation in patients with symptom-free rhinitis, 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.
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.  

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 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, 16 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. 36-49 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. 53 However, rhinitis in subjects without asthma is a risk factor for asthma both in adults 51 and children. 54 In adulthood, the development of asthma in patients with rhinitis is often independent of allergy, 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. 58 Severe chronic upper airway disease, as proposed by a joint ARIA–Global Allergy and Asthma European Network (GA2LEN)–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)–GA2LEN-ARIA expert group. 53

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), across diseases (eg, eosinophils in asthma), and in relation to comorbidities. 55 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-GA2LEN 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). 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. Pragmatic randomized trials have found that the guideline-based management of AR is more effective than free treatment choice. Nonetheless, the ARIA guideline panel believes that the recommendations reflect the best current treatment of patients with AR.

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. 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.

**DISSEMINATION AND IMPLEMENTATION**

Guidelines need simplicity and educational outputs (ie, Web-based activities [www.whiar.org, www.ariaespanol.org], pocket guides, and questionnaires), which are essential to facilitate implementation. 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.

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

**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. Measures of AR control include symptom scores, visual analog scale scores, quality-of-life scores, or scores with several items. 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 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 H1-antihistamine and corticosteroid 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. 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 H1-antihistamines. It is important for pharmacists to advise patients. Management of the allergic child at school is also important.

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.
TABLE I. ARIA statements, position papers, and recommendations

- European Academy of Allergy and Clinical Immunology: “Requirements for medications commonly used in AR treatment.”
- GA²LEN–World Allergy Organization: “Unmet needs in severe chronic upper airway disease (SCUAD).”
- GA²LEN–WHO Collaborating Center: “Uniform definition of asthma severity, control, and exacerbations: document presented for the WHO Consultation on Severe Asthma.”
- GA²LEN–WHO Collaborating Center: “Practical guide for skin prick tests in allergy to aeroallergens.”
- Mechanisms of the Development of Allergy (MeDALL)–GA²LEN–WHO Collaborating Center: Severe chronic allergic (and related) diseases: a uniform approach (accepted for publication).
- GA²LEN: “How to design and evaluate RCTs in immunotherapy for allergic rhinitis.”

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.

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}

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

*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 chairperson (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) 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. 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.

REFERENCES

13. Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: al-
1. J Allergy Clin Immunol 2010;126;466-76.
20. Van Hoecke H, Vasteseager N, Dewulf L, Sys L, van Cauwenberge P. Classifica-
tion and management of allergic rhinitis patients in general practice during pollen season. Allergy 2006;61:705-11.
sloratadine relieves nasal congestion and improves quality-of-life in persistent al-
lergic rhinitis. Allergy 2009;64:1663-70.
30. Al Sayadi M, Fedorowicz Z, Alhassimi D, Jamal A. Topical nasal steroids for in-
31. Nasser M, Fedorowicz Z, Aljufairi H, McKerrow W. Antihistamines used in ad-
32. Calderon MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Aller-
gen-specific immunotherapy for respiratory allergies: from meta-analysis to regis-
37. Arbes SJ Jr, Ginger PJ, Elliott L, Zeldin DC. Prevalences of positive skin test re-
sponses to 10 common allergens in the US population: results from the third Na-
38. Connell JT. Quantitative intranasal pollen challenges. 3. The priming effect in al-


APPENDIX 1. AUTHORS’ INSTITUTIONAL AFFILIATIONS

Reviewers: C. S. Ang, MD, A. K. Baigenzhin, MD, D. A. Boakye, PhD, A. H. Briggs, PhD, P. G. Burney, MD, W. W. Busse, MD, A. G. Chuchalin, MD, H. Haddad, MD, S. L. Johnston, MD, M. Kogevinas, MD, M. L. Levy, MD, A. Mohammad, MD, S. Oddie, PhD, D. Rezagui, MD, I. Terreehorst, MD, and J. O. Warner, MD

From 1University Hospital, Hôpital Arnaud de Villeneuve, Department of Respiratory Diseases, Montpellier, France; 2Inserm, CESP Centre for Research in Epidemiology and Population Health, U1018, Respiratory and Environmental Epidemiology team, Villejuif, France; 3the Departments of Clinical Epidemiology & Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada; 4the Department of Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Warsaw, Warsaw, Poland; 5University Hospital of Montpellier–Inserm U657, Hôpital Arnaud de Villeneuve, Montpellier, France; 6Research Centre in Respiratory Medicine (CIMER), Faculty of Medicine, Catholic University, Cordoba, Argentina; 7School of Specialization, Respiratory Medicine,
Manchester, United Kingdom; 83 the Department of Respiratory Diseases, Aarhus University Hospital, Aarhus, Denmark; 84 the Department of Dermatology and Allergy Biederstein, Technische Universität München, München, and the Division of Environmental Dermatology and Allergy Helmholtz Center/TUM, München, Germany; 85 the Division of Pulmonology, Asthma and Allergology, Chest Diseases Department, University Hospital of Strasbourg, Strasbourg, France; 86 the Romanian Society of Allergy and Clinical Immunology, University of Medicine, and Pharmacy Iuliu Hatieganu, Allergy Department, 3rd Medical Clinic, Cluj-Napoca, Romania; 87 the Department of Medicine, Director, Division of Clinical Immunology and Allergy, Michael G. DeGroote School of Medicine, Faculty of Health Sciences, McMaster University, AllerGen NCE, Hamilton, Ontario, Canada; 88 UPRES EA 220, Université Versailles Saint Quentin, Hopital Foch, Suresnes, France; 89 Service de pneumo-allergologie, Centre Hospitalier de la Région d’Annecy, Annecy, France; 90 University Clinic of Pulmonology and Allergy, University “Ss. Cyril and Methodius,” Skopje, Macedonia; 91 Georgia Health Sciences University, Augusta, Ga; 92 Service de pneumo-allergologie, Centre Hospitalo-Universitaire de Béni-Messous, Algiers, Algeria; 93 Vilnius University Faculty of Medicine, Lithuania, GA LEN Collaborating Centre; 94 the National Heart and Lung Institute, Imperial College, London, United Kingdom; 95 Allergy and Immunology, Wake Forest University School of Medicine, Winston-Salem, NC; 96 the Pediatric Allergy and Immunology Unit, Children’s Hospital, Ain Shams University, and the Egyptian Society of Pediatric Allergy and Immunology, Cairo, Egypt; 97 Société Marocaine des Maladies Respiratoires, Derb Ghellaf, and the Centre of Respiratory Diseases and Allergy, Casablanca, Morocco; 98 Vilnius University Faculty of Medicine, Vilnius, Lithuania; 99 Melloni Paediatrica, University of Milan Medical School at the Melloni Hospital, Milan, Italy; 100 Education for Health, Warwick, United Kingdom; 101 Dokkyo Medical University, Mibu, Tochigi, Japan; 102 World Health Organization Country Office in Georgia, Tbilisi, Georgia; 103 Allergia e Immunologia, Clinica Riccardo Palma, Lima, Peru; 104 the Faculty of Medicine, University of Nuevo León (UANL), Allergy and Clinical Immunology, Hospital Universitario, Monterrey, Mexico; 105 the Center of Allergy and Immunology, Tbilisi, Georgia; 106 the Immunology and Allergology Division, Department of Medicine, Clinical Hospital University of Chile, Santiago, Chile; 107 the Department of Otorhinolaryngology—Head and Neck Surgery, University Hospitals Leuven, Leuven, Belgium; 108 the Center of Public Health and Quality Improvement, Central Region of Denmark, Aarhus, Denmark; 109 Allergy Centre Vienna West, Vienna, Austria; 110 the Department of Paediatrics and Child Health, University College Cork, Cork, Ireland; 111 Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; 112 Université Paris-Sud, Service de Pneumologie, Hôpital Antoine-Béclère, AP-HP, INSERM U999, Clamart, France; 113 the Immunology Department, School of Medicine, del Salvador University, Buenos Aires, Argentina; 114 Medical and Biological Sciences, University of St Andrews, St Andrews, United Kingdom; 115 Groupe Hospitalier Trousseau-La Roche-Guyon, Centre de l’Asthme et des Allergies, APHP, Université Paris, Paris, France; 116 Hacettepe University School of Medicine, Pediatric Allergy and Asthma Unit, Hacettepe, Ankara, Turkey; 117 George Washington University School of Medicine, Washington, DC, and the Institute for Asthma and Allergy, Chevy Chase, Md; 118 Hacettepe University Hospital, Department of Chest Diseases Adult Allergy Unit, Sihiyye-Ankara, Turkey; 119 the Institute of Social Medicine, Epidemiology and Health Economics, Charité—Universitätsmedizin Berlin, Berlin, Germany; 120 McMaster University, Hamilton, Ontario, Canada; 121 Service de Pneumologie et de Réanimation Médicale, Hôtel-Dieu de France, and Faculté de Médecine, Université Saint-Joseph, Beirut, Lebanon; 122 the National Medical Center, Seoul, Korea; 123 Seoul National University, Seoul, Korea; 124 Korea Asthma Allergy Foundation, Seoul, Korea; 125 Service des Maladies Respiratoires, Centre Hospitalier Universitaire, Abidjan, Ivory Coast; 126 the Department of Pediatric Pulmonology and Pediatric Allergy, Beatrix Children’s Hospital, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; 127 the Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, Lodz, Poland; 128 the Department of Clinical Science and Education, Karolinska Institutet, and Sachs Childrens Hospital, Stockholm, Sweden; 129 the Center of Pulmonology and Allergy, Vilnius University, and Vilnius University Hospital “Santariskiu klinikos,” Vilnius, Lithuania; 130 the Allergy Department, Hospital Médica Sur, Mexico City, Mexico; 131 the University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam; 132 Hôpital du Sacré-Coeur de Montréal and University of Montreal, Montreal, Quebec, Canada; 133 the State Key Laboratory of Respiratory Diseases, First Affiliated Hospital of Guangzhou Medical College, Guangzhou, China; 134 the University of Tennessee College of Medicine, Memphis, Tenn; 135 the Asthma and Allergy Research Group, Ninewells Hospital, University of Dundee, Dundee, Scotland; 136 Dubai health authority and University of Sharjah, Sharjah, United Arab Emirates; 137 the Department of Allergy, Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland; 138 Compiègne, Association Franco-Vietnamienne de Pneumologie; 139 the Division of Clinical Immunology and Allergy, University of Mississippi Medical Center, Jackson, Miss; 140 the Arizona Respiratory Center, College of Medicine, and the BIO5 Institute, University of Arizona, Tucson, Ariz; 141 the Chronic Respiratory Diseases Research Center and National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Science, Tehran, Iran; 142 the Department of Dermatology and Allergy, Charité—Universitätsmedizin Berlin, Berlin, Germany; 143 Maputo Central Hospital, Department of Paediatrics, and Eduardo Mondlane University, Faculty of Medicine, Maputo, Mozambique; 144 the Unit of Pediatric Allergy and Pneumology, Children’s Hospital La Fe, Valencia, Spain; 145 the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; 146 Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm, Sweden; 147 the Allergy and Asthma Medical Group & Research Center, University of California, San Diego, Calif; 148 the Department of Allergy and Clinical Immunology, Centro Medico Nacional Siglo XXI, IMSS, Mexico City, Mexico; 149 the Dermatology Department, Aachen University, Aachen, Germany; 150 the Institute of Pneumology Marius Nasta, Bucharest, Romania; 151 Tishreen University School of Medicine, Department of Internal Medicine, WHO—EMRO Collaborating Center for Training and Research in Chronic Respiratory Diseases, Lattakia, Syria; 152 the Immunology Department, CUF-Descobertas Hospital, Lisbon, Portugal; 153 the Food Allergy Referral Centre Veneto
of Paediatrics and Child Health, Red Cross War Memorial Children’s Hospital, University of Cape Town, Cape Town, South Africa; 224 the Department of Otorhinolaryngology, School of Medicine, Catholic University of Córdoba, Córdoba, Argentina; 225 the Guangzhou Institute of Respiratory Diseases and State Key Laboratory of Respiratory Diseases, Guangzhou Medical College, Guangzhou, China; 226 the University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia; 227 the Pulmonology Research Institute and Russian University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; 228 the Department of Nutrition, National Heart and Lung Institute, Imperial College London, United Kingdom; 229 the Pulmonary Research Institute and Russian Respiratory Society, Moscow, Russia; 233 Association Franco-Libanaise de Pneumologie (AFLP) and Service de pneumologie, Centre Hospitalier Tarbes-Lourdes, Bigorre, France; 236 the National Heart and Lung Institute, Imperial College London, London, United Kingdom; 239 the National Heart and Lung Institute, Imperial College London, London, United Kingdom; 230 the National Heart and Lung Institute, Imperial College London, London, United Kingdom; 231 the Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; 232 the Department of Otorhinolaryngology, School of Medicine, University of Cape Town, Cape Town, South Africa; 233 Association Franco-Marocaine de Pathologie Thoracique (AFMAPATH), Marrakech, Morocco; 234 Bradford Neonatology, Bradford Royal Infirmary, Bradford, United Kingdom; 235 Association Franco-Algérienne de Pneumologie (AFAP); 236 the Department of Otorhinolaryngology and Paediatrics, AMC Hospital, Amsterdam, The Netherlands; 237 Association Franco-Marocaine de Pathologie Thoracique (AFMAPATH), Marrakech, Morocco; 238 the Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; 239 the National Heart and Lung Institute, Imperial College London, London, United Kingdom; 240 the Department of Otorhinolaryngology and Paediatrics, AMC Hospital, Amsterdam, The Netherlands; 241 Imperial College, London, and the Women and Children’s Clinical Programme Group, Imperial College Healthcare NHS Trust, St Mary’s Campus, London, United Kingdom.

Disclosure of potential conflict of interest: J. Bousquet has received honoraria from Stallergenes, Actelion, Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Merck, Novartis, OM Pharma, Sanofi, Teva, and Uriach. P. Demoly is a speaker for and on the advisory board of Stallergenes and ALK-Abelló; is a consultant for Therabel and Crucell; is a speaker for Merck/Schering-Plough, AstraZeneca, and GlaxoSmithKline; has received research support from Stallergenes and ALK-Abelló; and is the Vice President of the European Academy of Allergy and Clinical Immunology (EAACI). S. Bonini has a scientific board member and speaker at Symposia sponsored by A. Menarini, MSD & K, Novartis, Nycomed/Takeda, PHADIA/Thermo Fischer, and Stallergenes and is a member of the LIBRA (Italian Guidelines for Asthma, Rhinitis, and COPD) executive board. L. P. Boulet is on the advisory boards for AstraZeneca, GlaxoSmithKline, Merck, Novartis, and Novartis; has received lecture fees from 3M, AstraZeneca, GlaxoSmithKline, Merck, Novartis, and Novartis; has received research support from Altair, Amgen, Asmacare, AstraZeneca, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Pharmaxis, Schering, Wyeth, and Merck Frosst; is chair for the Canadian Thoracic Society Respiratory Guidelines Committee and the Global Initiative for Asthma (GINA) Guidelines and Implementation Committee; is an organizational holder for the Laval University Chair on Knowledge Transfer, Prevention and Education in Respiratory and Cardiovascular Health; and is a member of the Knowledge Translation Canada. T. B. Casale is on the Stallergenes advisory board, is a consultant for Roche has received research support from Stallergenes and Roche, and is Executive Vice President for the American Academy of Allergy, Asthma & Immunology (AAAAI). A. A. Cruz is an advisor and lecturer for Merck and Manteorp; is a lecturer for GlaxoSmithKline, Novartis, Chiesi, and Aventis; has received an educational grant from Ache; and has received research support from the Brazilian Research Council, Fundação de Amparo à Pesquisa da Bahia, and GlaxoSmithKline. W. J. Fokkens has received research support from GlaxoSmithKline and provided legal consultation/expert witness testimony for Stallergenes. J. A. Fonseca has received lecture and consulting fees from Merck has received research support from the Fundação Ciência e Tecnologia and is Vice President of the Sociedade Portuguesa de Alergologia e Imunologia Clinica. L. Grouse has received funds from Novartis for personal services. T. Haathela has received lecture fees from Abdi Ibrahim, GlaxoSmithKline, MSD, and OrionPharma and has received research support from Stallergenes. K. C. Lodrup Carlsen has received research support from MeDALL EU. R. Naclerio is on the speaker’s bureau for Merck and Sunovion; is a consultant for Teva, Kalypsys, and Regeneron; and has received research support from Nasonex, GlaxoSmithKline, Merck, and McNeal. K. Ohta has received lecture honoraria from MSD, Novartis, and GlaxoSmithKline. S. Palkonen’s employer received grants from Novartis, GlaxoSmithKline, Boehringer-Ingelheim, Pfizer, Chiesi, ALK-Abelló, Stallergenes, Nycomed, AstraZeneca, and Air Liquid Healthcare. N. G. Papadopoulos has received honoraria from Merck, Allergopharma, Abbott, and Uria. D. Price has received consultancy fees from Merck, Mundipharma, Novartis, GlaxoSmithKline, Almirall, Chiesi, Kyorin, and Teva; has received consultancy fees and grants from Pfizer, AstraZeneca, and Boehringer-Ingelheim; has received research support from the UK National Health Service, Aerocine, and Nycomed; holds shares in AKL Ltd; and is director of Research in Real Life Ltd. D. Ryan is a consultant for Uria and is Allergy Lead for the International Primary Care Respiratory Group. F. E. R. Simons is on the Rupatadine Medical Advisory Board. D. Williams’s spouse is employed by GlaxoSmithKline. A. Yorgancioglu has received honoraria from MSD, GlaxoSmithKline, and Novartis and has received research support from Chiesi. O. M. Yusuf has received honoraria from and is director and chair of research for the International Primary Care Respiratory Group. C. A. Afdad has received research support from Novartis, PREDICTA, Swiss National Science Foundation, MeDALL, the Global Allergy and Asthma European Network (GA2LEN), and the Christine Kuthel Center for Allergy Research and Education; has provided legal consultation/expert witness testimony on the topics of Actellion Th2-specific receptors, Aventis T-cell and B-cell regulation, Stallergenes allergen-specific immunotherapy, and Allergopharma allergen-specific immunotherapy; is a Fellow and interest group member of the AAAAI; is president of the EAACI; and is a GA2LEN ex-com member WP leader. I. J. Ansotegui has received support from Novartis, PREDICTA, Swiss National Science Foundation, MeDALL, the Global Allergy and Asthma European Network (GA2LEN), and the Christine Kuthel Center for Allergy Research and Education; has provided legal consultation/expert witness testimony on the topics of Actellion Th2-specific receptors, Aventis T-cell and B-cell regulation, Stallergenes allergen-specific immunotherapy, and Allergopharma allergen-specific immunotherapy; is a Fellow and interest group member of the AAAAI; is president of the EAACI; and is a GA2LEN ex-com member WP leader. I. J. Ansotegui has received...
consulting fees and honoraria from Faes Farma and Bial, has received consulting fees from Johnson & Johnson and Sanofi, and has received honoraria from AstraZeneca. E. D. Bateman is a consultant for and on the advisory board of Almirall; is on the advisory board of Forest, Novartis, Napp Pharma, and Actelion; has received lecture and consultancy fees and grants and is on the advisory board for Boehringer Ingelheim; has received lecture fees and is on the advisory board for GlaxoSmithKline, Nycomed, and AstraZeneca; is a consultant for ALK-Abelló; and is the GINA chair of board. E. H. Bel has received research support from GlaxoSmithKline, Novartis, and Innovative Medicine Initiative (EU). M. S. Blais is a speaker for GlaxoSmithKline, Merck, AstraZeneca, Nycomed, Sunovion, and Genentech; is a consultant for Alcon, ISTA, Allergan, Proctor & Gamble, and Pfizer; has received research support from GlaxoSmithKline; and is HAD treasurer. M. A. Calderon is a speaker for ALK-Abelló, Merck, and STG. K. H. Carlsten has received research support from Helse Sør-Øst RHF (Southern and Eastern Norway Regional Health Authority). W. Carr is a consultant for and has received research support from MEDA, Alcon, and ISTA. A. M. Cepeda is a speaker for MSD, AstraZeneca, and Novartis and has received research support from Novartis and Universidad Metropolitana. L. Cox is a speaker for Thermo-Fisher and ISTA and has received research support from Stallergenes and Teva. A. Custovic has received lecture fees from GlaxoSmithKline, Thermo-Fisher, MSD, and Airsonett; is on the advisory board for Novartis; and has received research support from the Medical Research Council and Moulton Charitable Trust. R. Dahl has received lecture fees from ALK-Abelló and MSD, has received research support from ALK-Abelló and Stallergenes, and is chair of the Danish Respiratory Society. U. Darsow is a consultant for Benoard. F. De Blay has received research support from Stallergenes, ALK-Abelló, Novartis, GlaxoSmithKline, AB Science, and Amgen. J. A. Denburg has received research support from the Canadian Institutes for Health Research and AllerGen NCE. P. Devillier has received consultancy fees and honoraria from Stallergenes and has received consultancy fees from Merck/Schering-Plough, GlaxoSmithKline, and AstraZeneca. S. R. Durham is a consultant and speaker for ALK-Abelló and Merck, is a speaker for GlaxoSmithKline, has received consultancy fees from Boehringer Ingelheim and Circassia, has received research support from ALK-Abelló and Novartis, has provided legal consultation/expert witness testimony on the topic of topical corticosteroids and antihistamines in allergic rhinitis is on the Immune Tolerance Network/National Institute of Allergy and Infectious Diseases (NIAID) steering committee, and is on the British Society for Allergy and Clinical Immunology standards of care committee. M. S. Dykewicz is a consultant for Merck; is on the AAAAI Board of Directors, Needs Assessment Committee, Rhinitis/Sinusitis/Ocular Diseases Committee, and Web Site Oversight Committee; and is on the American College of Allergy, Asthma & Immunology (ACAAI) Program Directors Advisory Committee (chair), Annual Program Planning Committee, Publications Committee, Rhinitis-Sinusitis Committee, Occupational Health Committee, Ocular Allergy Committee. A. Fiochi has received research support from Stallergenes. S. Gonzalez Diaz is a speaker for GlaxoSmithKline, MSD, and Takeda and has received research support from the University Hospital and Medical School of Universidad Autonoma de Nuevo Leon, Mexico. M. Gotua has received honoraria from GlaxoSmithKline and AstraZeneca. J. O’B. Hourihane has received research support from the Children’s Research Foundation (Ireland), Danone, the Food Standards Agency (United Kingdom), and Stallergenes; in addition, his employer, University College Cork, holds a patent on challenge outcome predictor software. M. Humbert has received consultancy and lecture fees from AstraZeneca, GlaxoSmithKline, Novartis, Pfizer, Stallergenes, and Teva. J. C. Ivancevich is on the Faes Farma advisory board, is speaker for Laboratorios Casasco Argentina, and is Web editor for the World Allergy Organization and Interasma. O. Kalayci was the Uriach Pharma chairperson at the company sponsor symposium. M. A. Kaliner is a consultant for Istal and Alcon, has received research support from multiple allergy and asthma companies, and has provided legal consultation/expert witness testimony for Alcon. T. Keil has received research support from the European Union (EU) and DTG. P. K. Keith is a speaker for and has received research support from GlaxoSmithKline and Merck. B. Koff N’Goran is a speaker for AstraZeneca and GlaxoSmithKline. G. H. Koppelman has received research support from the Netherlands Asthma Foundation and MedDALL. D. E. Larenas-Linnemann has received a speaker’s fee and travel grant from Merck-Sharp-Dohme, Mexico; has received a speaker’s fee from AstraZeneca; has received travel grants from Allerquim Mexico, ALK-Abelló, and Stallergenes; has received research support from Allerquim Mexico, ALK-Abelló, Stallergenes, and Greer Laboratories; and is chair of the IT committee for the AAAAI and Mexican College of Clinical Immunology and Allergy. L. T. Le has received honoraria from GlaxoSmithKline and AstraZeneca, has received research support and honoraria from MSD, and is chair of the Respiratory Society of Ho Chi Minh City, Vietnam. C. Lemièreme is on the AstraZeneca advisory board. P. Lieberman is an advisor for the Allergy Foundation of America. B. Lipworth has provided legal consultation/expert witness testimony for Nycomed on the topic of nasal ciclesonide. B. Mahboub is employed by the Dubai Health Authority and the University of Sharjah. F. D. Martinez is a consultant for Medimmune and has received lecture honorarium and travel fees from Abbott. E. O. Meltzer is a consultant and on the advisory board for Alcon, AstraZeneca, Bausch + Lomb, Dey, Forest, Ista, Johnson & Johnson, Meda, Merck, ONO Pharma, OptiNose, Proctor & Gamble, Rady Children’s Hospital, Rigel, Sanofi Aventis, Sepracor, Stallergenes, Teva, Alexza, Boehringer Ingelheim, Kalypsos, and Sunovion; is a speaker for the AAAAI, Alcon, Allergists for Israel, Dey, Florida Asthma Immunol Society, Ista, Sepracor, Teva, Merck, and Sunovion; has received research support from Aman, Apotex, HRA, MedImmune, Schering-Plough, Alcon, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Proctor & Gamble, Sunovion (Sepracor), and Teva; has provided legal consultation/expert witness testimony for Aventis Pharmaceuticals and Sanofi Aventis in the USLLC v. Barr Laboratories Fexofenadine Litigation; and is a Fellow of the AAAAI, ACAAI, and World Allergy Organization (WAO). H. Merk has received research support from Phadia and has provided legal consultation/expert witness testimony for Novartis and ALK-Abelló. F. Mihaltan has received consulting fees and honoraria from AstraZeneca, GlaxoSmithKline, MSD, Novartis, Nycomed, Boehringer Ingelheim, Servier, Sanofi, Pfizer, CSCI Johnson & Johnson, Oxyzen Plus, and New Medicins. S. Nafti has received research support from the European Respiratory Society and the Société de Pneumologie de Langue Française Asthma and has provided legal consultation/expert witness testimony for GlaxoSmithKline on the topics of asthma and chronic obstructive pulmonary disease. Y. Okamoto is a medical advisory
for Taibo Pharmaceutical Co, Ono Pharmaceutical Co, and Meiji
Nyugyo Co and has received research support from the Ministry of
Health, Welfare, and Labor. D. S. Postma has received consult-
ty fees from Nycomed, GlaxoSmithKline, AstraZeneca, and
Chiesi. K. F. Rabe has received research support from Altana, No-
vartis, AstraZeneca, and MSD and has provided legal consulta-
tion/expert witness testimony for AstraZeneca, Chiesi, Novartis,
MSD, and GlaxoSmithKline. J. Ring has received research sup-
port from ALK-Abelló, Allergopharma, Almirall-Hermal, Astel-
las, Bencard, Biogen-Idec, Gladerma, GlaxoSmithKline, Leo,
MSD, Novartis, Phadia, PLS Design, and Stallergenes. R. Roberts
is president of the World Organization of Family Doctors and the
American Academy of Family Physicians Foundation and is Vice
Chair of the Interstate Postgraduate Medical Association. B. Ro-
gala has received lecture fees from Takeda, Nycomed, Teva,
UCB, and Chiesi and is on the advisory board for MSD and Astra-
Zeneca. G. K. Scadding has received research support from and is
a speaker for ALK-Abelló and GlaxoSmithKline, is on the Uriach
advisory board, and is a speaker for Merck. A. Sheikh has received
consultancy fees from Phadia and NAPP and is a Royal College of
GPs Clinical Champion in Allergy. S. W. Stoloff is a consultant
and on the advisory board for Teva and is a consultant for Aero-
crine, Merck, and Sunovion. B. P. Yawn has received research sup-
port from the Agency for Healthcare Research and Quality
(AHRQ) and the National Heart, Lung, and Blood Institute
(NHLBI). T. Zuberbier has received consultancy fees, honoraria,
and/or research support from Ansell, Bayer Schering, OST, Fuji-
sawa, IHAL, Henkel, Kryolan, Leti, MSO, Novartis, Procter and
Gamble, Sanofi-Aventis, Schering-Plough, Stallergenes, and
UCB; is on the Scientific Advisory Board for the German Society
for Allergy and Clinical Immunology; is on the Expert Commis-
sion “Novel Food” of the German Federal Ministry of Consumer
Protection; is Head of the European Centre for Allergy Research
Foundation (ECARF); is a Committee member of the World
Health Organization (WHO) Initiative Allergic Rhinitis and its
Impact on Asthma (ARIA); is a Member or the WAO Communica-
tions Council; and is Secretary General of GA²LEN. The rest of
the authors declare that they have no relevant conflicts of interest.