

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



Jean Bousquet, MD,^{a,b} Holger J. Schünemann, MD,^c Akdis Togias, MD,^{d*} Claus Bachert, MD,^e Martina Erhola, MD,^f Peter W. Hellings, MD,^g Ludger Klimek, MD,^h Oliver Pfaar, MD,ⁱ Dana Wallace, MD,^j Ignacio Ansotegui, MD,^k Ioana Agache, MD,^l Anna Bedbrook, BSc,^a Karl-Christian Bergmann, MD,^m Mike Bewick, MD,ⁿ Philippe Bonniaud, MD,^o Sinthia Bosnic-Anticevich, PhD,^p Isabelle Bossé, MD,^q Jacques Bouchard, MD,^r Louis-Philippe Boulet, MD,^s Jan Brozek, MD,^c Guy Brusselle, MD,^t Moises A. Calderon, MD,^u Walter G. Canonica, MD,^v Luis Caraballo, MD,^w Vicky Cardona, MD,^x Thomas Casale, MD,^y Lorenzo Cecchi, MD,^z Derek K. Chu, MD,^c Elisio M. Costa, PhD,^{aa} Alvaro A. Cruz, MD,^{bb} Wienczyslawa Czarlewski, MD,^{cc} Gennaro D'Amato, MD,^{dd} Philippe Devillier, MD,^{ee,ff} Mark Dykewicz, MD,^{gg} Motohiro Ebisawa, MD,^{hh} Jean-Louis Fauquert, MD,ⁱⁱ Wytske J. Fokkens, MD,^{jj} Joao A. Fonseca, MD,^{kk} Jean-François Fontaine, MD,^{ll} Bilun Gemicioglu, MD,^{mmm} Roy Gerth van Wijk, MD,ⁿⁿ Tari Haahtela, MD,^{oo} Susanne Halken, MD,^{pp} Despo Ierodiakonou, MD,^{qq} Tomohisa Inuma, MD,^{rr} Juan-Carlos Ivancevich, MD,^{ss} Marek Jutel, MD,^{tt} Igor Kaidashev, MD,^{uu} Musa Khaitov, MD,^{vv} Omer Kalayci, MD,^{www} Jorg Kleine Tebbe, MD,^{ssss} Marek L. Kowalski, MD,^{xxx} Piotr Kuna, MD,^{yy} Violeta Kvedariene, MD,^{zz} Stefania La Grutta, MD,^{aaa} Désirée Larenas-Linnemann, MD,^{bbb} Susanne Lau, MD,^{ccc} Daniel Laune, PhD,^{ddd} Lan Le, MD,^{eee} Philipp Lieberman, MD,^{fff} Karin C. Lodrup Carlsen, MD,^{ggg} Olga Lourenço, PhD,^{hhh} Gert Marien, MD,ⁱⁱⁱ Pedro Carreiro-Martins, MD,^{jjj} Erik Melén, MD,^{kkk} Enrica Menditto, PhD,^{lll} Hugo Neffen, MD,^{mmm} Gregoire Mercier, MD,ⁿⁿⁿ Ralph Mosges, MD,^{ooo} Joaquim Mullol, MD,^{ppp} Antonella Muraro, MD,^{qqq} Leyla Namazova, MD,^{rrr} Ettore Novellino, PhD,^{sss} Robyn O'Hehir, MD,^{ttt} Yoshitaka Okamoto, MD,^{rrr} Ken Ohta, MD,^{tttt} Hae Sim Park, MD,^{uuu} Petr Panzner, MD,^{vvv} Giovanni Passalacqua, MD,^{wwww} Nhan Pham-Thi, MD,^{xxx} David Price, FRCP,^{yyy} Graham Roberts, MD,^{zzz} Nicolas Roche, MD,^{aaaa} Christine Rolland, BSc,^{bbbb} Nelson Rosario, MD,^{cccc} Dermot Ryan, MD,^{dddd} Boleslaw Samolinski, MD,^{eeee} Mario Sanchez-Borges, MD,^{fff} Glenis K. Scadding, MD,^{gggg} Mohamed H. Shamji, MD,^{hhhh} Aziz Sheikh, MD,ⁱⁱⁱⁱ Ana-Maria Todo Bom, MD,^{jjjj} Sanna Toppila-Salmi, MD,^{kkkk} Ioana Tsiligianni, MD,^{qq} Marilyn Valentin-Rostan, MD,^{llll} Arunas Valiulis, MD,^{mmmm} Erkka Valovirta, MD,ⁿⁿⁿⁿ Maria-Teresa Ventura, MD,^{oooo} Samantha Walker, MD,^{pppp} Susan Wasserman, MD,^{qqqq} Arzu Yorgancioglu, MD,^{rrrr} and Torsten Zuberbier, MD,^m the Allergic Rhinitis and Its Impact on Asthma Working Group

Montpellier, Villejuif, Montigny

le Bretonneux, Dijon, La Rochelle, Levallois, Suresnes, Clermont-Ferrand, Reims, and Paris, France; Brussels, Leuven, and Ghent, Belgium; Berlin, Wiesbaden, Marburg, Hamburg, and Cologne, Germany; Hamilton, Ontario, Canada; Bethesda, Md; Helsinki and Turku, Finland; Fort Lauderdale and Tampa, Fla; Erandio and Barcelona, Spain; Brasov, Romania; London, Southampton, and Edinburgh, United Kingdom; Glebe and Melbourne, Australia; Quebec City, Quebec, Canada; Milan, Prato, Naples, Palermo, Padua, Genoa, and Bari, Italy; Cartagena, Colombia; Porto, Covilhã, Lisbon, and Coimbra, Portugal; Bahia and Parana, Brazil; St Louis, Mo; Sagamiyara, Chiba, and Tokyo, Japan; Amsterdam and Rotterdam, The Netherlands; Istanbul, Ankara, and Manisa, Turkey; Odense, Denmark; Crete, Greece; Buenos Aires and Santa Fe, Argentina; Wroclaw, Lodz, and Warsaw, Poland; Poltava, Ukraine; Moscow, Russia; Vilnius, Lithuania; Mexico City, Mexico; Ho Chi Minh City, Vietnam; Germantown, Tenn; Oslo, Norway; Stockholm, Sweden; Suwon, South Korea; Pilsen, Czech Republic; Singapore; Caracas, Venezuela; and Montevideo, Uruguay

From ^aMACVIA-France, Fondation Partenariale FMC VIA-LR, Montpellier; ^bVIMA, INSERM U 1168, VIMA: Ageing and chronic diseases Epidemiological and public health approaches, Villejuif, Université Versailles St-Quentin-en-Yvelines, UMR-S 1168, Montigny le Bretonneux, Euforea, Brussels, and Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin; ^cthe Department of Health Research Methods, Evidence, and Impact, Division of Immunology and

Allergy, McMaster University, Hamilton; ^dthe Division of Allergy, Immunology, and Transplantation (DAIT), National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda; ^ethe Upper Airways Research Laboratory, ENT Department, Ghent University Hospital, Ghent; ^fthe National Institute for Health and Welfare, Helsinki; ^gthe Department of Otorhinolaryngology, University Hospitals Leuven, and Academic Medical Center, University of Amsterdam, and Euforea, Brussels; ^hthe Center for Rhinology and Allergology, Wiesbaden; ⁱthe Department of

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

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,

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

symptom severity, and multimorbidity; (3) efficacy and safety of treatment¹; (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 devised⁵ and digitalized⁶ to step up or step down allergic rhinitis treatment based on control. However, its

Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg; ¹Nova Southeastern University, Fort Lauderdale; ²the Department of Allergy and Immunology, Hospital Quirónsalud Bizkaia, Erandio; ³the Faculty of Medicine, Transylvania University, Brasov; ⁴Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Comprehensive Allergy-Centre, Department of Dermatology and Allergy, member of GA²LEN, Berlin; ⁵IQ4U Consultants, London; ⁶CHU Dijon; ⁷the Woolcock Institute of Medical Research, University of Sydney and Woolcock Emphysema Centre and Sydney Local Health District, Glebe; ⁸Allergist, La Rochelle; ⁹Laval University, Quebec City; ¹⁰the Quebec Heart and Lung Institute, Laval University, Quebec City; ¹¹the Department of Respiratory Medicine, Ghent University Hospital, Ghent; ¹²Imperial College London–National Heart and Lung Institute, Royal Brompton Hospital NHS, London; ¹³Personalized Medicine Clinic Asthma & Allergy, Humanitas University, Humanitas Research Hospital, Rozzano, Milan; ¹⁴the Institute for Immunological Research, University of Cartagena, Campus de Zaragocilla, Edificio Biblioteca Primer Piso, and the Foundation for the Development of Medical and Biological Sciences (Fundemeb), Cartagena; ¹⁵the Allergy Section, Department of Internal Medicine, Hospital Vall d’Hebron & ARADyAL research network, Barcelona; ¹⁶the Division of Allergy/Immunology, University of South Florida, Tampa; ¹⁷SOS Allergology and Clinical Immunology, USL Toscana Centro, Prato; ¹⁸UCIBIO, REQUIMTE, Faculty of Pharmacy, and Competence Center on Active and Healthy Ageing of University of Porto (AgeUPNetWork), University of Porto; ¹⁹ProAR–Núcleo de Excelencia em Asma, Federal University of Bahia, and the WHO GARD Planning Group, Brazil; ²⁰Medical Consulting Czarlewski, Levallois; ²¹the Division of Respiratory and Allergic Diseases, Hospital “A Cardarelli,” University of Naples Federico II, Naples; ²²UPRES EA220, Pôle des Maladies des Voies Respiratoires, Hôpital Foch, Université Paris-Saclay, Suresnes; ²³the Allergy and Clinical Immunology Section, National Heart and Lung Institute, Imperial College London; ²⁴the Section of Allergy and Immunology, Saint Louis University School of Medicine, Saint Louis; ²⁵the Clinical Research Center for Allergy and Rheumatology, Sagamiara National Hospital, Sagamiara; ²⁶Unité de pneumo-allergologie de l’enfant, pôle pédiatrique Pr-Labbé, CHU de Clermont-Ferrand-Estaing, Clermont-Ferrand; ²⁷the Department of Otorhinolaryngology, Amsterdam University Medical Centres, AMC, Amsterdam; ²⁸CINTEISIS, Center for Research in Health Technology and Information Systems, Faculdade de Medicina da Universidade do Porto, and Medida, Porto; ²⁹Allergist, Reims; ³⁰the Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul; ³¹the Department of Internal Medicine, section of Allergy, Erasmus MC, Rotterdam; ³²the Skin and Allergy Hospital, Helsinki University Hospital, and University of Helsinki, Helsinki; ³³Hans Christian Andersen Children’s Hospital, Odense University Hospital, Odense; ³⁴the Department of Social Medicine, Faculty of

Medicine, University of Crete and International Primary Care Respiratory Group, Crete; ³⁵the Department of Otorhinolaryngology, Chiba University Hospital, Chiba; ³⁶Servicio de Alergia e Inmunología, Clínica Santa Isabel, Buenos Aires; ³⁷the Department of Clinical Immunology, Wrocław Medical University, Wrocław; ³⁸Ukrainina Medical Stomatological Academy, Poltava; ³⁹the National Research Center, Institute of Immunology, Federal Medicobiological Agency, Laboratory of Molecular immunology, Moscow; ⁴⁰the Pediatric Allergy and Asthma Unit, Hacettepe University School of Medicine, Ankara; ⁴¹the Department of Immunology and Allergy, Healthy Ageing Research Center, Medical University of Lodz; ⁴²the Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz; ⁴³the Institute of Biomedical Sciences, Department of Pathology, Faculty of Medicine, Vilnius University and Institute of Clinical medicine, Clinic of Chest diseases and Allergology, Faculty of Medicine, Vilnius University, Vilnius; ⁴⁴the Institute of Biomedicine and Molecular Immunology (IBIM), National Research Council (CNR), Palermo; ⁴⁵the Center of Excellence in Asthma and Allergy, Médica Sur Clinical Foundation and Hospital, México City; ⁴⁶the Department of Paediatric Pneumology, Immunology and Intensive Care, Charité Universitätsmedizin, Berlin; ⁴⁷KYomed IN-NOV, Montpellier; ⁴⁸the University of Medicine and Pharmacy, Ho Chi Minh City; ⁴⁹the Departments of Internal Medicine and Pediatrics (Divisions of Allergy and Immunology), University of Tennessee College of Medicine, Germantown; ⁵⁰Oslo University Hospital, Department of Paediatrics, Oslo, and University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Oslo; ⁵¹the Faculty of Health Sciences and CICS–UBI, Health Sciences Research Centre, University of Beira Interior, Covilhã; ⁵²Euforea, Belgium; ⁵³Hospital de Dona Estefânia, Centro Hospitalar de Lisboa Central, EPE, Lisbon, and Nova Medical School, CEDOC, Integrated Pathophysiological Mechanisms Research Group, Lisbon; ⁵⁴Sachs’ Children and Youth Hospital, Södersjukhuset, Stockholm and Institute of Environmental Medicine, Karolinska Institutet, Stockholm; ⁵⁵CIRFF, Center of Pharmacoeconomics, University of Naples Federico II, Naples; ⁵⁶Center of Allergy, Immunology and Respiratory Diseases, Santa Fe, and the Center for Allergy and Immunology, Santa Fe; ⁵⁷Unité Médico-Economie, Département de l’Information Médicale, University Hospital, Montpellier; ⁵⁸the Institute of Medical Statistics, and Computational Biology, Medical Faculty, University of Cologne, and Clinical Research International, Hamburg; ⁵⁹the Rhinology Unit & Smell Clinic, ENT Department, Hospital Clinic, and Clinical & Experimental Respiratory Immunology, IDIBAPS, CIBERES, University of Barcelona; ⁶⁰Food Allergy Referral Centre Veneto Region, Department of Women and Child Health, Padua General University Hospital, Padua; ⁶¹the Scientific Centre of Children’s Health under the MoH, Moscow, and Russian National Research Medical University named Pirogov, Moscow; ⁶²Department of Pharmacy of University of Naples Federico II, Naples; ⁶³the Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Central Clinical School, Monash University, Melbourne, and the

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

Department of Immunology, Monash University, Melbourne; ^{uuu}the Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon; ^{vvv}the Department of Immunology and Allergology, Faculty of Medicine in Pilsen, Charles University in Prague, Pilsen; ^{www}Allergy and Respiratory Diseases, Ospedale Policlinico San Martino—University of Genoa; ^{xxx}the Allergy Department, Pasteur Institute, Paris; ^{yyy}the Observational and Pragmatic Research Institute, Singapore; ^{zzz}David Hide Centre, St Mary's Hospital, Isle of Wight, and University of Southampton, Southampton; ^{aaaa}Pneumologie et Soins Intensifs Respiratoires, Hôpitaux Universitaires Paris, and Hôpital Cochin; ^{bbbb}Association Asthme et Allergie, Paris; ^{cccc}Hospital de Clinicas, University of Parana; ^{dddd}Allergy and Respiratory Research Group, University of Edinburgh, Edinburgh; ^{eecc}the Department of Prevention of Environmental Hazards and Allergology, Medical University of Warsaw; ^{ffff}the Allergy and Clinical Immunology Department, Centro Medico-Docente La Trinidad, Caracas; ^{gggg}the Royal National TNE Hospital, University College London; ^{hhhh}the Immunomodulation and Tolerance Group and Allergy and Clinical Immunology, Imperial College London, London; ⁱⁱⁱⁱthe Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh; ^{jjjj}Imunoloogia, Centro Hospitalar Universitário de Coimbra and Faculty of Medicine, University of Coimbra; ^{kkkk}the Skin and Allergy Hospital, Helsinki University Hospital and University of Helsinki, Helsinki; ^{llll}Allergist, Montevideo; ^{mmmm}Vilnius University Institute of Clinical Medicine, Clinic of Children's Diseases, and Institute of Health Sciences, Department of Public Health, Vilnius, and the European Academy of Paediatrics (EAP/UEMS-SP), Brussels; ⁿⁿⁿⁿthe Department of Lung Diseases and Clinical Immunology, University of Turku and Terveystalo Allergy Clinic, Turku; ^{oooo}the University of Bari Medical School, Unit of Geriatric Immunology, Bari; ^{pppp}Asthma UK, London; ^{qqqq}the Department of Medicine, Clinical Immunology and Allergy, McMaster University, Hamilton; ^{rrrr}the Department of Pulmonary Diseases, Celal Bayar University, Faculty of Medicine, Manisa; ^{ssss}Allergy & Asthma Center Westend, Outpatient & Clinical Research Center, Berlin; and ^{tttt}National Hospital Organization, Tokyo National Hospital, Tokyo.

*Dr Togiias' coauthorship of this publication does not constitute endorsement by the US National Institute of Allergy and Infectious Diseases or any other United States government agency.


Disclosure of potential conflict of interest: J. Bousquet reports personal fees and other support from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach and other support from KYomed INNOV outside the submitted work. C. Bachert reports fees from ALK-Abelló, Mylan, Stallergenes, Novartis, Sanofi, GlaxoSmithKline, and AstraZeneca outside the submitted work. P. W. Hellings reports grants and personal fees from Mylan during the conduct of the study and personal fees from Sanofi, Allergopharma, and Stallergenes outside the submitted work. D. Wallace reports and indicates that she is the cochair of the Joint Task Force on Practice Parameters, a task force composed of 12 members of the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology. I. Ansoategui reports personal fees from Mundipharma, Roxall, Sanofi, MSD, Faes Farma, Hikma, UCB, and AstraZeneca outside the submitted work. S. Bosnic Anticevich reports grants from TEVA and personal fees from TEVA, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Sanofi, and Mylan outside the submitted work. L. P. Boulet reports research grants for participation in multicentre studies from AIM Therapeutics, Amgen, Asmacure, AstraZeneca, Axikin, GlaxoSmithKline, Hoffman La Roche, Novartis, Ono Pharma, Sanofi, and Takeda; support for research projects introduced by the investigator from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, and Takeda; support for consulting and advisory boards from AstraZeneca, Novartis, and Methapharm; royalties as a coauthor of "UpToDate" (occupational asthma); nonprofit grants for production of educational materials from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Frosst, and Novartis; conference fees from AstraZeneca, GlaxoSmithKline, Merck, and Novartis; and support for participation in conferences and meetings from Novartis and Takeda and has served as past president and member of the Canadian Thoracic Society Respiratory Guidelines Committee; Chair of the Board of Directors of the Global Initiative for Asthma (GINA); Chair of the Global Initiative for Asthma (GINA) Guidelines Dissemination and Implementation Committee; Laval University Chair on Knowledge Transfer, Prevention and Education in Respiratory and Cardiovascular Health; members of scientific committees for the American College of Chest Physicians, American Thoracic Society, European Respiratory Society, and World Allergy Organization; and 1st Vice-President of the Global Asthma Organization INTERASMA outside the submitted work. M. A. Calderon reports personal fees (advisory and/or lecture honorarium) from ALK-Abelló, ALK-US, Stallergenes Greer, HAL-Allergy,

Allergopharma, and ASIT Biotech outside the submitted work. L. Cecchi reports personal fees from Menarini and Malesci and personal fees and nonfinancial support from ALK-Abelló outside the submitted work. P. Devillier reports fees from Boehringer Ingelheim, AstraZeneca, Stallergenes Greer, ALK-Abelló, Novartis, GlaxoSmithKline, Chiesi, Menarini, Unither, IQVIA, Yslab, and Top Pharm outside the submitted work. T. Haahela reports lecturing fees from Mundipharma and Orion Pharma during the conduct of the study. S. Halcken reports other from ALK-Abelló outside the submitted work. J. C. Ivancevich reports personal fees from Faes Farma and Eurofarma Argentina, other support from Laboratorios Casasco, and personal fees and other support from Sanofi outside the submitted work. J. Kleine Tebbe reports personal fees from AllergenOnline, Allergy Therapeutics, Allergopharma, Bencard, HAL Allergy, Dr Pflieger, Lofarma, Merck US, AstraZeneca, Sanofi Genentech, Stallergenes-Greer, Thieme Publishers, Thermo Fisher Scientific, Springer International Publishers, InfectoPharm, LETI, and GlaxoSmithKline; grants and personal fees from ALK-Abelló and Novartis; and nonfinancial support from WHO/UIS Allergen Nomenclature Subcommittee outside the submitted work. S. Lau reports personal fees from DBV, personal fees from Allergopharma, grants and personal fees from ALK-Abelló, and personal fees from Sanofi-Genzyme outside the submitted work. R. Mosques reports personal fees from ALK-Abelló, Allergopharma, Allergy Therapeutics, Friulchem, Hexal, Servier, FAES, Klosterfrau, Bayer, GlaxoSmithKline, Johnson&Johnson, Meda, Stada, UCB, Nuvo, Menarini Mundipharma, Pohl-Boskamp, from Hikma; grants and personal fees from Bencard and Stallergenes; grants from Leti, Optima, BiotopAG, Hulka, and Ursapharm; personal fees and nonfinancial support from Lofarma and Novartis; and nonfinancial support from Roxall, Atmos, Bionorica, Otonomy, and Ferrero outside the submitted work. Y. Okamoto reports personal fees from Shionogi, Torii, GlaxoSmithKline, and MSD; grants and personal fees from Kyorin, Kyowa, and Eizai; grants and personal fees from Tihoo; grants from Yakuruto and Yamada Bee Farm; and grants from ASIT Biotech. D. Price reports grants from AKL Research and Development, the British Lung Foundation, and UK National Health Service; personal fees from Amgen, Cipla, GlaxoSmithKline, Kyorin, and Merck; grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, the Respiratory Effectiveness Group, Sanofi Genzyme, Teva, Theravance, and Zentiva (Sanofi Generics); nonfinancial support from the Efficacy and Mechanism Evaluation Programme and Health Technology Assessment outside the submitted work; and stock/stock options from AKL Research and Development, which produces phytopharmaceuticals and holds ownership of 74% of the social enterprise Optimum Patient Care (Australia and UK) and 74% of Observational and Pragmatic Research Institute (Singapore). M. H. Shamji reports grants from ALK-Abelló, Regeneron, Merck, and the Immune Tolerance Network; personal fees from ASIT Biotech and Allergopharma; and grants and personal fees from ALK-Abelló outside the submitted work. A. Todo Bom reports grants and personal fees from Novartis, Mundipharma, GlaxoSmithKline, and Teva Pharma; personal fees from AstraZeneca; and grants from Boehringer Ingelheim, Sanofi, and Leti outside the submitted work. I. Tsiligianni reports personal fees from honoraria for educational activities, speaking engagements, and advisory boards from Boehringer Ingelheim and Novartis and a grant from GlaxoSmithKline outside the submitted work. S. Wasserman reports other support from CSL Behring, Shire, AstraZeneca, Teva, Meda, Merck, GlaxoSmithKline, Novartis, PEDIAPHARM, Aralez, Sanofi, and Stallergenes outside the submitted work. T. Zuberbier reports organizational affiliation with the WHO initiative Allergic Rhinitis and Its Impact on Asthma and is a member of the board of the German Society for Allergy and Clinical Immunology (DGAKI); serves as head of the European Centre for Allergy Research Foundation (ECARF), Secretary General: Global Allergy and Asthma European Network (GA2-LEN); and is a member of the Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 1, 2019; revised May 7, 2019; accepted for publication June 12, 2019.

Available online October 15, 2019.

Corresponding author: Jean Bousquet, MD, CHU Arnaud de Villeneuve, 371 Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France. E-mail: jean.bousquet@orange.fr.

 The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2019.06.049>



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*, Société 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

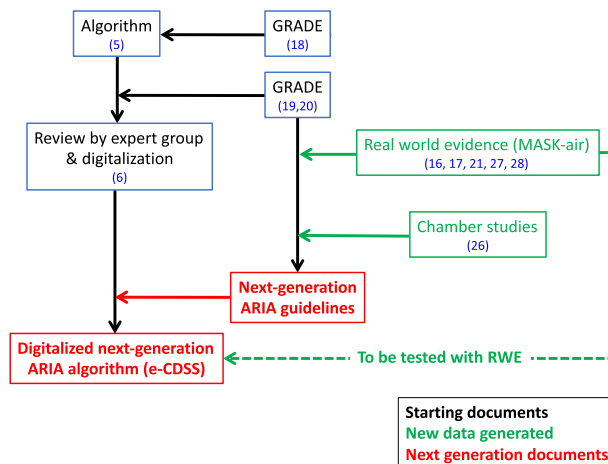


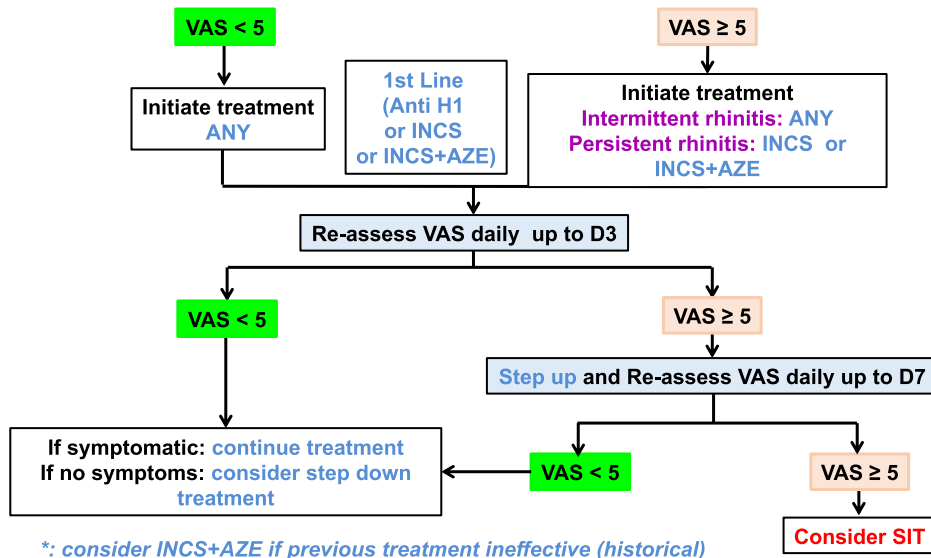
FIG 2. Development of next-generation ARIA guidelines.

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 Vieillessement 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

A Assessment of control in untreated symptomatic patient



B Assessment of control in treated symptomatic patient

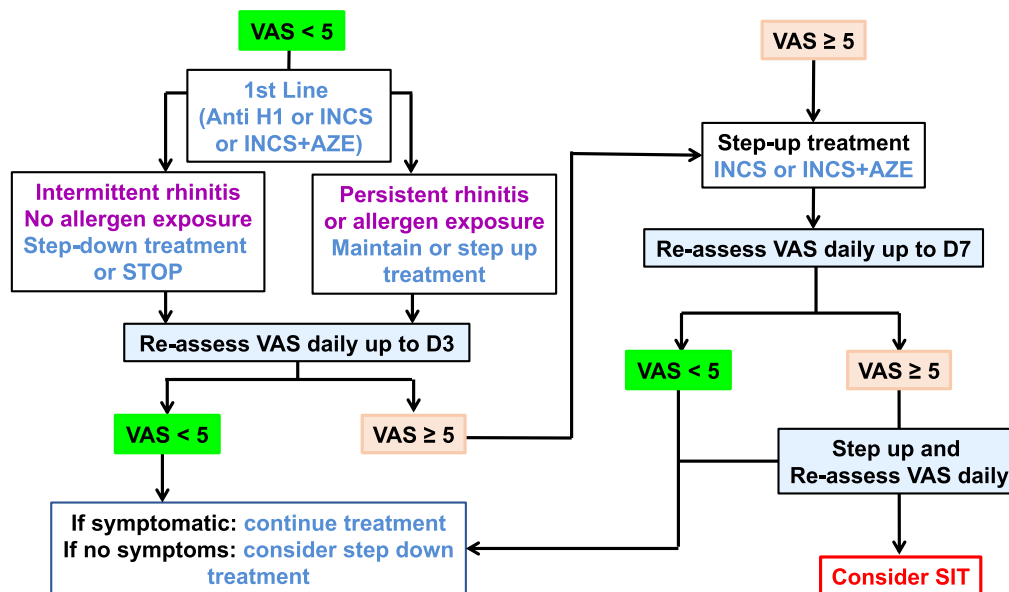


FIG 3. A, Step-up algorithm in untreated patients using VASs (adolescents and adults).⁵ The proposed algorithm considers the treatment steps and the patient's preference. VAS levels are shown in ratios. If ocular symptoms remain once treatment has been initiated, add intraocular treatment. B, Step-up 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 rhinitis⁶

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 reviews¹ 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 2016²¹ and US Practice Parameters 2017²² 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 revision²¹ and US Practice Parameters 2017²² 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	<ol style="list-style-type: none"> 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. <p><i>For all of these recommendations, the level of evidence was low²⁻³ or very low.^{1,4}</i></p>
US practice parameters 2017 ²²	<p>For initial treatment of nasal symptoms of SAR in patients ≥12 years of age, clinicians:</p> <ul style="list-style-type: none"> ● should routinely prescribe monotherapy with an INCS rather than a combination of an INCS and an oral H₁-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 H₁-antihistamines have a slower onset of action. Intranasal corticosteroids (INCSs; alone or with oral H₁-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 H₁-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 furoate or levocabastine	No data for fluticasone 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 study²³ 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 scenarios⁶

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.

- When physicians are allergic, they behave like patients,⁵⁸ suggesting the need for behavioral science to improve control.
- Patients who do not take medications usually have well-controlled symptoms.^{23,24}
- 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.
- Patients reporting oral H₁-antihistamine monotherapy have a poorer level of control than those reporting INCS-containing medications.^{23,24}
- Most patients have a worse control level with increasing medications,^{23,24} contradicting guidelines that propose to increase the treatment level to achieve control.
- 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 H₁-antihistamines with INCSs was not found to be more effective than INCSs alone.
- The combination of intranasal H₁-antihistamines with INCSs was found to be more effective than INCSs alone.
- Intranasal H₁-antihistamine-containing medications are effective within minutes.

NEXT-GENERATION ARIA ALGORITHM

The overall ARIA algorithm⁵ was found to be appropriate, and no change is needed. The step-up and step-down approach proposed by ARIA experts⁶ 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

REFERENCES

1. Meltzer EO, Wallace D, Dykewicz M, Shneyer L. Minimal clinically important difference (MCID) in allergic rhinitis: Agency for Healthcare Research and quality or anchor-based thresholds? *J Allergy Clin Immunol Pract* 2016;4:682-8.e6.
2. Munoz-Cano R, Ribo P, Araujo G, Giralt E, Sanchez-Lopez J, Valero A. Severity of allergic rhinitis impacts sleep and anxiety: results from a large Spanish cohort. *Clin Transl Allergy* 2018;8:23.
3. Vandeplass O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, et al. Impact of rhinitis on work productivity: a systematic review. *J Allergy Clin Immunol Pract* 2018;6:1274-86.e9.
4. Meltzer EO. Pharmacotherapeutic strategies for allergic rhinitis: matching treatment to symptoms, disease progression, and associated conditions. *Allergy Asthma Proc* 2013;34:301-11.
5. Bousquet J, Schunemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A, et al. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. *J Allergy Clin Immunol* 2016;138:367-74.e2.
6. Courbis AL, Murray RB, Arnavielhe S, Caimmi D, Bedbrook A, Van Eerd M, et al. Electronic Clinical Decision Support System for allergic rhinitis management: MASK e-CDSS. *Clin Exp Allergy* 2018;48:1640-53.

7. Use of real-world evidence to support regulatory decision-making for medical devices. Guidance for industry and Food and Drug Administration staff document issued on August 31, 2017. Bethesda: US Food and Drug Administration, US Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health Center for Biologics Evaluation and Research; 2017.
8. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-world evidence—what is it and what can it tell us? *N Engl J Med* 2016; 375:2293-7.
9. Briere JB, Bowrin K, Taieb V, Millier A, Toumi M, Coleman C. Meta-analyses using real-world data to generate clinical and epidemiological evidence: a systematic literature review of existing recommendations. *Curr Med Res Opin* 2018;34:2125-30.
10. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy* 2009;64:669-77.
11. Brozek JL, Akl EA, Compalati E, Kreis J, Terracciano L, Fiocchi A, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. *Allergy* 2011; 66:588-95.
12. Brozek JL, Akl EA, Jaeschke R, Lang DM, Bossuyt P, Glasziou P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines: part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. *Allergy* 2009;64:1109-16.
13. Oyinlola JO, Campbell J, Kousoulis AA. Is real world evidence influencing practice? A systematic review of CPRD research in NICE guidances. *BMC Health Serv Res* 2016;16:299.
14. Bousquet J, Lund VJ, Van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, et al. Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. *Allergy* 2003;58:733-41.
15. Bousquet J, Bodez T, Gehano P, Klossek JM, Liard F, Neukirch F, et al. Implementation of guidelines for allergic rhinitis in specialist practices. A randomized pragmatic controlled trial. *Int Arch Allergy Immunol* 2009;150: 75-82.
16. Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) phase 4 (2018): change management in allergic rhinitis and asthma multimorbidity using mobile technology. *J Allergy Clin Immunol* 2019;143:864-79.
17. Transformation of health and care in the digital single market is gaining more support. Available at: ec.europa.eu/digital-single-market/en/news/transformation-health-and-care-digital-single-market-gaining-more-support. Accessed September 26, 2019.
18. Bousquet J, Arnavielhe S, Bedbrook A, Bewick M, Laune D, Mathieu-Dupas E, et al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. *Clin Transl Allergy* 2018;8:45.
19. Bousquet J, Anto JM, Annesi-Maesano I, Dedeu T, Dupas E, Pepin JL, et al. POLLAR: Impact of air POLLution on Asthma and Rhinitis; a European Institute of Innovation and Technology Health (EIT Health) project. *Clin Transl Allergy* 2018;8:36.
20. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466-76.
21. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. *J Allergy Clin Immunol* 2017;140:950-8.
22. Dykewicz MS, Wallace DV, Baroody F, Bernstein J, Craig T, Finegold I, et al. Treatment of seasonal allergic rhinitis: an evidence-based focused 2017 guideline update. *Ann Allergy Asthma Immunol* 2017;119:489-511.e41.
23. Bousquet J, Devillier P, Arnavielhe S, Bedbrook A, Alexis-Alexandre G, van Eerd M, et al. Treatment of allergic rhinitis using mobile technology with real-world data: the MASK observational pilot study. *Allergy* 2018;73:1763-74.
24. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Mobile technology offers novel insights on control and treatment of allergic rhinitis. The MASK study. *J Allergy Clin Immunol* 2019;144:135-43.e6.
25. Allergic rhinitis: developing drug products for treatment. Guidance for industry. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) September 2018. Available at: www.fda.gov/media/71158/download. Accessed September 26, 2018.
26. Patel P, Patel D. Efficacy comparison of levocetirizine vs montelukast in ragweed sensitized patients. *Ann Allergy Asthma Immunol* 2008;101:287-94.
27. Stubner P, Ziegelmayer R, Horak F. A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit—the Vienna Challenge Chamber (VCC). *Curr Med Res Opin* 2004;20:891-902.
28. Klimek L, Bergmann KC, Biedermann T, Bousquet J, Hellings P, Jung K, et al. Visual analogue scales (VAS): measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: position paper of the German Society of Allergy (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergy and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHOKHC). *Allergo J Int* 2017;26:16-24.
29. Horak F, Bruttman G, Pedrali P, Weeke B, Frolund L, Wolff HH, et al. A multicentric study of loratadine, terfenadine and placebo in patients with seasonal allergic rhinitis. *Arzneimittelforschung* 1988;38:124-8.
30. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol* 2010;105:168-73.
31. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol* 2012;129:1282-9.e10.
32. Kaszuba SM, Baroody FM, deTineo M, Haney L, Blair C, Naclerio RM. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. *Arch Intern Med* 2001; 161:2581-7.
33. Glacy J, Putnam K, Godfrey S, Falzon L, Mauger B, Samson D, et al. Treatments for Seasonal Allergic Rhinitis. AHRQ comparative effectiveness reviews. Rockville (MD): AHRQ; 2013.
34. Guideline on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis. European Medicine Agency. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-development-medicinal-products-treatment-allergic-rhino-conjunctivitis_en.pdf. Accessed September 26, 2019.
35. Katial RK, Salapatek AM, Patel P. Establishing the onset of action of intranasal corticosteroids: is there an ideal study design? *Allergy Asthma Proc* 2009;30: 595-604.
36. Pfaar O, Calderon MA, Andrews CP, Angjeli E, Bergmann KC, Bonlokke JH, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future—an EAACI position paper. *Allergy* 2017;72:1035-42.
37. Ellis AK, Jacobs RL, Tenn MW, Steacy LM, Adams DE, Walker TJ, et al. Clinical standardization of two controlled allergen challenge facilities—the environmental exposure unit and the biogenics research chamber. *Ann Allergy Asthma Immunol* 2019;122:639-46.e2.
38. Bousquet J, Meltzer EO, Couroux P, Koltun A, Kopietz F, Munzel U, et al. Onset of action of the fixed combination intranasal azelastine-fluticasone propionate in an allergen exposure chamber. *J Allergy Clin Immunol Pract* 2018;6:1726-32.
39. Patel P, D'Andrea C, Sacks HJ. Onset of action of azelastine nasal spray compared with mometasone nasal spray and placebo in subjects with seasonal allergic rhinitis evaluated in an environmental exposure chamber. *Am J Rhinol* 2007;21:499-503.
40. Patel P, Roland PS, Marple BF, Benninger PJ, Margalies H, Brubaker M, et al. An assessment of the onset and duration of action of olopatadine nasal spray. *Otolaryngol Head Neck Surg* 2007;137:918-24.
41. Patel P, Patel D, Kunjibettu S, Hall N, Wingertzahn MA. Onset of action of ciclesonide once daily in the treatment of seasonal allergic rhinitis. *Ear Nose Throat J* 2008;87:340-53.
42. Salapatek AM, Lee J, Patel D, D'Angelo P, Liu J, Zimmerer RO Jr, et al. Solubilized nasal steroid (CDX-947) when combined in the same solution nasal spray with an antihistamine (CDX-313) provides improved, fast-acting symptom relief in patients with allergic rhinitis. *Allergy Asthma Proc* 2011;32:221-9.
43. Horak F, Jager S, Toth J, Berger U. Efficacy and tolerability of astemizole-D and Loratadine-D during prolonged, controlled allergen challenge in the Vienna Challenge Chamber. *Arzneimittelforschung* 1996;46:1077-81.
44. Horak F, Jager S, Berger U. Onset and duration of the effects of three antihistamines in current use—astemizole, loratadine and terfenadine forte—studied during prolonged, controlled allergen challenges in volunteers. *J Int Med Res* 1992;20:422-34.
45. Horak F, Ziegelmayer UP, Ziegelmayer R, Kavina A, Marschall K, Munzel U, et al. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. *Curr Med Res Opin* 2006;22:151-7.
46. Horak F, Ziegelmayer R, Ziegelmayer R, Lemell P. The effects of bilastine compared with cetirizine, fexofenadine, and placebo on allergen-induced nasal and ocular symptoms in patients exposed to aeroallergen in the Vienna challenge chamber. *Inflamm Res* 2010;59:391-8.
47. Ziegelmayer UP, Horak F, Toth J, Marks B, Berger UE, Burtin B. Efficacy and safety of an oral formulation of cetirizine and prolonged-release pseudoephedrine

- versus budesonide nasal spray in the management of nasal congestion in allergic rhinitis. *Treat Respir Med* 2005;4:283-7.
48. Stubner UP, Toth J, Marks B, Berger UE, Burtin B, Horak F. Efficacy and safety of an oral formulation of cetirizine and prolonged-release pseudoephedrine versus xylometazoline nasal spray in nasal congestion. *Arzneimittelforschung* 2001;51:904-10.
 49. Horak F, Stubner UP, Ziegelmayer R, Harris AG. Effect of desloratadine versus placebo on nasal airflow and subjective measures of nasal obstruction in subjects with grass pollen-induced allergic rhinitis in an allergen-exposure unit. *J Allergy Clin Immunol* 2002;109:956-61.
 50. Murdoch RD, Bareille P, Ignar D, Miller SR, Gupta A, Boardley R, et al. The improved efficacy of a fixed-dose combination of fluticasone furoate and levocabastine relative to the individual components in the treatment of allergic rhinitis. *Clin Exp Allergy* 2015;45:1346-55.
 51. Stuebner P, Horak F, Ziegelmayer R, Arnaiz E, Leuratti C, Perez I, et al. Effects of rupatadine vs placebo on allergen-induced symptoms in patients exposed to aeroallergens in the Vienna challenge chamber. *Ann Allergy Asthma Immunol* 2006;96:37-44.
 52. mHealth. New horizons for health through mobile technologies. Global Observatory for eHealth series—Vol 3 WHO Library Cataloguing-in-Publication Data. Available at: http://www.who.int/goe/publications/goe_mhealth_web.pdf. Accessed September 26, 2019.
 53. Sleurs K, Seys S, Bousquet J, Fokkens W, Gorris S, Pugin B, et al. Mobile health tools for the management of chronic respiratory diseases. *Allergy* 2019;74:1292-306.
 54. Bousquet J, Hellings PW, Agache I, Bedbrook A, Bachert C, Bergmann KC, et al. ARIA 2016: care pathways implementing emerging technologies for predictive medicine in rhinitis and asthma across the life cycle. *Clin Transl Allergy* 2016;6:47.
 55. Bousquet J, Agache I, Aliberti MR, Angles R, Annesi-Maesano I, Anto JM, et al. Transfer of innovation on allergic rhinitis and asthma multimorbidity in the elderly (MACVIA-ARIA)—EIP on AHA Twinning Reference Site (GARD research demonstration project). *Allergy* 2018;73:77-92.
 56. Bousquet J, Bedbrook A, Czarlewski W, Onorato GL, Arnavielhe S, Laune D, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. *Clin Transl Allergy* 2019;9:16.
 57. Menditto E, Costa E, Midao L, Bosnic-Anticevich S, Novellino E, Bialek S, et al. Adherence to treatment in allergic rhinitis using mobile technology. The MASK Study. *Clin Exp Allergy* 2019;49:442-60.
 58. Bousquet J, Murray R, Price D, Somekh D, Munter L, Phillips J, et al. The allergic allergist behaves like a patient. *Ann Allergy Asthma Immunol* 2018;121:741-2.
 59. Nagarajan N, Jalal D. Resistant hypertension: diagnosis and management. *Adv Chronic Kidney Dis* 2019;26:99-109.
 60. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol* 2009;124:428-33.
 61. Bousquet J, Caimmi DP, Bedbrook A, Bewick M, Hellings PW, Devillier P, et al. Pilot study of mobile phone technology in allergic rhinitis in European countries: the MASK-rhinitis study. *Allergy* 2017;72:857-65.
 62. Caimmi D, Baiz N, Tanno LK, Demoly P, Arnavielhe S, Murray R, et al. Validation of the MASK-rhinitis visual analogue scale on smartphone screens to assess allergic rhinitis control. *Clin Exp Allergy* 2017;47:1526-33.
 63. Bousquet J, Arnavielhe S, Bedbrook A, Fonseca J, Morais Almeida M, Todo Bom A, et al. The Allergic Rhinitis and its Impact on Asthma (ARIA) score of allergic rhinitis using mobile technology correlates with quality of life: the MASK study. *Allergy* 2018;73:505-10.
 64. Bousquet J, Devillier P, Anto JM, Bewick M, Haahtela T, Arnavielhe S, et al. Daily allergic multimorbidity in rhinitis using mobile technology: a novel concept of the MASK study. *Allergy* 2018;73:1622-31.
 65. Bousquet J, VandenPlas O, Bewick M, Arnavielhe S, Bedbrook A, Murray R, et al. The Work Productivity and Activity Impairment Allergic Specific (WPAI-AS) questionnaire using mobile technology: the MASK study. *J Investig Allergol Clin Immunol* 2018;28:42-4.
 66. Bonini M. Electronic health (e-Health): emerging role in asthma. *Curr Opin Pulm Med* 2017;23:21-6.
 67. Pizzulli A, Perna S, Florack J, Pizzulli A, Giordani P, Tripodi S, et al. The impact of telemonitoring on adherence to nasal corticosteroid treatment in children with seasonal allergic rhinoconjunctivitis. *Clin Exp Allergy* 2014;44:1246-54.
 68. Miller TA. Health literacy and adherence to medical treatment in chronic and acute illness: a meta-analysis. *Patient Educ Couns* 2016;99:1079-86.
 69. Batterham RW, Hawkins M, Collins PA, Buchbinder R, Osborne RH. Health literacy: applying current concepts to improve health services and reduce health inequalities. *Public Health* 2016;132:3-12.
 70. Hellings PW, Borrelli D, Pietikainen S, Agache I, Akdis C, Bachert C, et al. European Summit on the Prevention and Self-Management of Chronic Respiratory Diseases: report of the European Union Parliament Summit (29 March 2017). *Clin Transl Allergy* 2017;7:49.

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 H₁-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 H₁-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 H₁-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 H₁-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 ≥ 70% and PDC ≤ 1.25).

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

REFERENCES

- E1. Sleurs K, Seys S, Bousquet J, Fokkens W, Gorris S, Pugin B, et al. Mobile health tools for the management of chronic respiratory diseases. *Allergy* 2019;74:1292-306.
- E2. Bousquet J, Hellings PW, Agache I, Bedbrook A, Bachert C, Bergmann KC, et al. ARIA 2016: care pathways implementing emerging technologies for predictive medicine in rhinitis and asthma across the life cycle. *Clin Transl Allergy* 2016;6:47.
- E3. Bousquet J, Anto JM, Annesi-Maesano I, Dedeu T, Dupas E, Pepin JL, et al. POLLAR: Impact of air POLLution on Asthma and Rhinitis; a European Institute of Innovation and Technology Health (EIT Health) project. *Clin Transl Allergy* 2018;8:36.
- E4. Bousquet J, Caimmi DP, Bedbrook A, Bewick M, Hellings PW, Devillier P, et al. Pilot study of mobile phone technology in allergic rhinitis in European countries: the MASK-rhinitis study. *Allergy* 2017;72:857-65.
- E5. Bousquet J, Chavannes NH, Guldmond N, Haahtela T, Hellings PW, Sheikh A. Realising the potential of mHealth to improve asthma and allergy care: how to shape the future. *Eur Respir J* 2017;49.
- E6. Caimmi D, Baiz N, Tanno LK, Demoly P, Arnavielhe S, Murray R, et al. Validation of the MASK-rhinitis visual analogue scale on smartphone screens to assess allergic rhinitis control. *Clin Exp Allergy* 2017;47:1526-33.
- E7. Bousquet J, Arnavielhe S, Bedbrook A, Alexis-Alexandre G, Eerd MV, Murray R, et al. Treatment of allergic rhinitis using mobile technology with real world data: the MASK observational pilot study. *Allergy* 2018;73:1763-77.
- E8. Bousquet J, Devillier P, Anto JM, Bewick M, Haahtela T, Arnavielhe S, et al. Daily allergic multimorbidity in rhinitis using mobile technology: a novel concept of the MASK study. *Allergy* 2018;73:1622-31.
- E9. Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW, et al. MACVIA-ARIA Sentinel Network for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation. *Allergy* 2015;70:1372-92.
- E10. Bouret R, Bousquet J, Mercier J, Camuzat T, Bedbrook A, Demoly P, et al. MASK rhinitis, a single tool for integrated care pathways in allergic rhinitis. *World Hosp Health Serv* 2015;51:36-9.
- E11. Bousquet J, Arnavielhe S, Bedbrook A, Bewick M, Laune D, Mathieu-Dupas E, et al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. *Clin Transl Allergy* 2018;8:45.
- E12. Bousquet J, Agache I, Aliberti MR, Angles R, Annesi-Maesano I, Anto JM, et al. Transfer of innovation on allergic rhinitis and asthma multimorbidity in the elderly (MACVIA-ARIA)—EIP on AHA Twinning Reference Site (GARD research demonstration project). *Allergy* 2018;73:77-92.
- E13. Bousquet J, Bedbrook A, Czarlewski W, Onorato GL, Arnavielhe S, Laune D, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. *Clin Transl Allergy* 2019;9:16.
- E14. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Mobile technology offers novel insights on control and treatment of allergic rhinitis: the MASK study. *J Allergy Clin Immunol* 2019;144:135-43.e6.
- E15. Menditto E, Costa E, Midao L, Bosnic-Anticevich S, Novellino E, Bialek S, et al. Adherence to treatment in allergic rhinitis using mobile technology. The MASK Study. *Clin Exp Allergy* 2019;49:442-60.

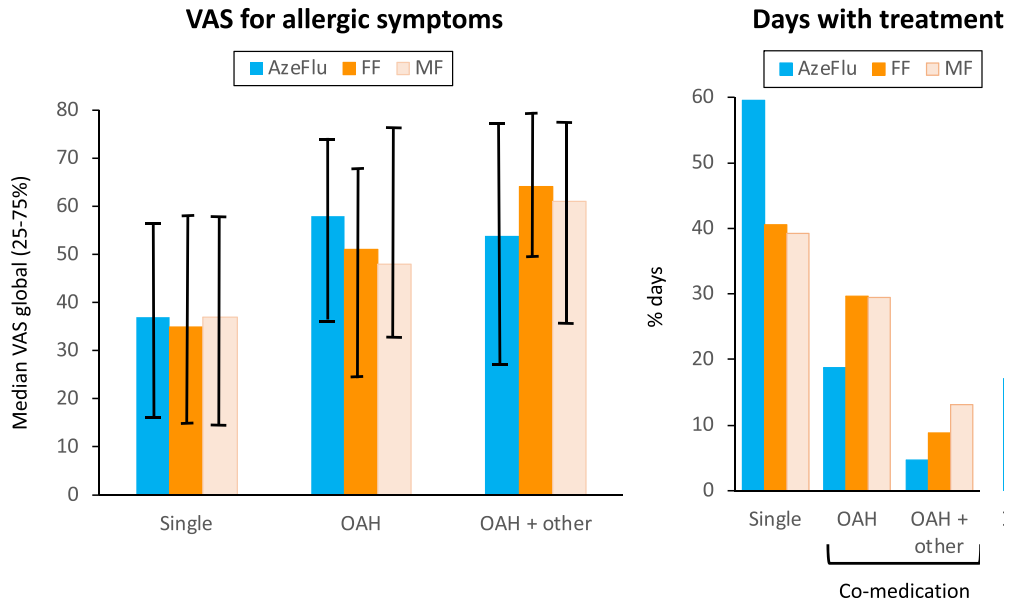


FIG E1. Efficacy of INCS-containing medications (VAS global) and percentage of days with comedication. *FF*, Fluticasone furoate; *MF*, mometasone furoate; *OAH*, oral H₁-antihistamine; *Other*, any other medication; *Single*, no comedication.