Toward personalization of asthma treatment according to trigger factors

Katarzyna Niespodziana, PhD,[a] Kristina Borochova, MSc,[a] Petra Pazderova, MSc,[a] Thomas Schlederer, PhD,[a] Natalia Astafyeva, MD, PhD,[b] Tatiana Baranovskaya, MD,[c] Mohamed-Ridha Barbouche, MD, PhD,[d] Evgeny Beltyukov, MD, DSc,[e] Angelika Berger, MD,[f] Elena Borzova, MD, PhD,[g,h,i] Jean Bousquet, MD,[j,k,l] Roxana S. Bumbacea, MD, PhD,[m] Snezhana Bychkovskaya, MD,[n] Luis Caraballo, MD,[o] Kian Fan Chung, MD, DSc, FRCP,[p,q] Adnan Custovic, MD, PhD, FRCP, FAAAI,[p,q] Guillermo Docena, PhD,[r] Thomas Eiwegger, MD,[s,t,u] Irina Evsegneeva, MD,[v] Alexander Emelyanov, MD, PhD,[w] Peter Errhalt, MD,[x] Rustem Fassakhov, MD, PhD,[y] Rezeda Fayzullina, MD, DSc,[z] Elena Fedenko, MD, PhD,[aa] Daria Fomina, MD, PhD,[v,bb] Zhongshan Gao, PhD,[cc] Pedro Giavina-Bianchi, MD, PhD,[dd] Maia Gotua, MD, PhD,[ee] Susanne Greber-Platzer, MD, MBA,[ff] Gunilla Hedlin, MD, PhD,[gg,hh] Natalia Ilina, MD,[aa] Zhanat Ispayeva, MD, PhD,[ii] Marco Idzko, MD,[jj] Sebastian L. Johnston, MD, PhD,[p,q] Ömer Kalayci, MD,[kk] Alexander Karaulov, MD, PhD,[v] Antonina Karsonova, MD, PhD,[v] Musa Khaitov, MD, DSc,[aa] Elena Kovzel, MD, PhD,[ll] Marek L. Kowalski, MD, PhD,[mm] Dmitry Kudlay, MD, PhD,[aa] Michael Levin, MD, PhD,[nn] Svetlana Makarova, PhD,[oo] Paolo Maria Matricardi, MD,[pp] Kari C. Nadeau, MD, PhD,[qq] Leyla Namazova-Baranova, MD,[rr] Olga Naumova, MD, PhD,[ss] Oleksandr Nazarenko, MD, PhD,[tt] Paul M. O'Byrne, MB, BCh, FRCP(C),[uu] Faith Osier, MBChB, PhD,[vv] Alexander N. Pampura, MD, PhD,[ww] Carmen Panaitescu, MD, PhD,[xx] Nikolaos G. Papadopoulos, MD, PhD,[yy,zz] Hae-Sim Park, MD,[aaa] Ruby Pawankar, MD, PhD, FRCP, FAAAAI,[bbb] Wolfgang Pohl, MD,[ccc] Harald Renz, MD,[ddd] Ksenja Riabova, MD,[v] Vanitha Sampath, PhD,[qq] Bülent E. Sekerel, MD,[kk] Elopy Sibanda, MD, PhD,[eee,fff] Valérie Siroux, PhD,[ggg] Ludmila P. Sizyakina, MD, PhD,[hhh] Jin-Lyu Sun, MD, PhD,[iii] Zsolt Szepfalusi, MD,[ff] Tetiana Umanets, PhD,[jjj] Hugo P. S. Van Bever, MD, PhD,[kkk] Marianne van Hage, MD,[lll] Margarita Vasileva, CMS,[mmm] Erika von Mutius, MD, MSc,[nnn,ooo,ppp] Jiu-Yao Wang, MD, PhD,[qqq] Gary W. K. Wong, MD,[rrr] Sergii Zaikov, MD,[sss] Mihaela Zidarn, MD, PhD,[ttt,uuu] and Rudolf Valenta, MD, PhD[a,v,aa,vvv,www]

Vienna and Krems, Austria; Saratov, Ekaterinburg, Moscow, Kransnoyarsk, St Petersburg, Kazan, Ufa, Rostov, and Khabarovsk, Russia; Minsk, Belarus; Tunis, Tunisia; Montpellier, Paris, and Grenoble, France; Bucharest, Romania; Cartagena de Indias, Colombia; London and Manchester, United Kingdom; La Plata, Argentina; Toronto and Hamilton, Ontario, Canada; Hangzhou, Beijing, and Hong Kong, China; Sao Paulo, Brazil; Tbilisi, Georgia; Stockholm, Sweden; Almaty and Nur-Sultan, Kazakhstan; Ankara, Turkey; Lodz, Poland; Cape Town, South Africa; Berlin, Marburg, and Munich, Germany; Stanford, Calif; Kyiv, Ukraine; Kilifi, Kenya; Timisoara, Romania; Athens, Greece; Suwon, Korea; Tokyo, Japan; Harare and Bulawayo, Zimbabwe; Singapore, Singapore; Tainan, Taiwan; and Golnik and Ljubljana, Slovenia

From [a]the Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna; [b]the Department of Clinical Immunology and Allergology of Saratov State Medical University, Saratov; [c]the Belarusian Medical Academy of Post Diploma Studies, Minsk; [d]the Department of Immunology, Institut Pasteur de Tunis, Tunis; [e]the Department of Faculty Therapy, Endocrinology, Allergology and Immunology, Ural State Medical University, Ekaterinburg; [f]the Division of Neonatology, Pediatric Intensive Care and Neuropediatrics, Department of Pediatrics and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna; [g]the Department of Clinical Allergology and Immunology, Russian Medical Academy of Continuous Professional Education, Moscow; [h]the Department of Clinical Genetics, Research and Clinical Institute for Pediatrics named after Yuri Veltischev at the Pirogov Russian National Research Medical University, Moscow; [i]the Department of Dermatology and Venereology, I.V. Sechenov First State Medical University, Moscow; [j]the University Hospital, Montpellier; [k]the MACVIA-France, Montpellier; [l]the Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin; [m]the Department of Allergology and Clinical Immunology, University of Medicine and Pharmacy "Carol Davila," Bucharest; [n]the Department of Pediatrics, Krasnoyarsk Medical University, Kransnoyarsk; [o]the Institute for Immunological Research, The University of Cartagena, Cartagena de Indias; [p]the National Heart & Lung Institute, Imperial College London, London; [q]the MRC and Asthma UK Centre in Allergic Mechanisms of Asthma, London; [r]Facultad de Ciencias Exactas, Universidad Nacional de La Plata, La Plata; [s]the Translational Medicine Program, Research Institute, Hospital for Sick Children, Toronto, Ontario; [t]the Department of Immunology, University of Toronto, Toronto, Ontario; [u]the Division of Immunology and Allergy, Food Allergy and Anaphylaxis Program, Hospital for Sick Children, Departments of Paedriatrics and Immunology, University of Toronto, Toronto, Ontario; [v]the Laboratory of Immunopathology, Department of Clinical Immunology and Allergy, Sechenov First Moscow State Medical University, Moscow; [w]the Department of Respiratory Medicine and Allergy, North-Western Medical University, St Petersburg; [x]the Department of Pneumology, University Hospital Krems and Karl Landsteiner University of Health Sciences, Krems; [y]the Institute of Fundamental Medicine and Biology of Kazan Federal University, Kazan; [z]the Faculty of Pediatrics, Bashkir State Medical University, Ufa; [aa]the NRC Institute of Immunology FMBA of Russia, Moscow; [bb]the City Moscow Center of Allergy and Immunology, Clinical Hospital No. 52, Moscow; [cc]the Allergy Research Center, Zhejiang University, Hangzhou; [dd]the Clinical Immunology and Allergy Division, University of Sao Paulo, Sao Paulo; [ee]the Center of Allergy and Immunology, David Tvildiani Medical University, Tbilisi; [ff]the Division of Pediatric Pulmonology, Allergology and Endocrinology, Department of Pediatrics and Adolescent Medicine, Comprehensive Center Pediatrics, Medical University of Vienna, Vienna; [gg]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm; [hh]the Department of Women's and Children's Health, Karolinska Institutet, Stockholm; [ii]the Allergology Department, Kazakh National Medical University, Almaty; [jj]the Department of Pneumology, Medical University of Vienna, Vienna; [kk]the Pediatric Allergy and Asthma Unit, Hacettepe University School of Medicine, Ankara; [ll]the Department of Clinical Immunology, Allergology, Pulmonology, Republic Diagnostic Center, Corporate Fund University

Asthma is a severe and chronic disabling disease affecting more than 300 million people worldwide. Although in the past few drugs for the treatment of asthma were available, new treatment options are currently emerging, which appear to be highly effective in certain subgroups of patients. Accordingly, there is a need for biomarkers that allow selection of patients for refined and personalized treatment strategies. Recently, serological chip tests based on microarrayed allergen molecules and peptides derived from the most common rhinovirus strains have been developed, which may discriminate 2 of the most common forms of asthma, that is, allergen- and virus-triggered asthma. In this perspective, we argue that classification of patients with asthma according to these common trigger factors may open new possibilities for personalized management of asthma. (J Allergy Clin Immunol 2020;145:1529-34.)

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Medical Center of Nazarbayev University, Nur-Sultan; [mm]the Department of Allergy and Immunology, Medical University Lodz, Lodz; [nn]the Division of Asthma and Allergy, University of Cape Town, Cape Town; [oo]the Department of Preventive Pediatrics, National Medical Research Center for Children's Health, Moscow; [pp]the Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Charité-University Medicine Berlin, Berlin; [qq]the Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Stanford University, Stanford; [rr]the Department of Pediatrics, Russian National Research Medical University of MoH RF, Moscow; [ss]the Center of Allergic Diseases of Upper Respiratory Ways, National Academy of Medical Sciences of Ukraine, Kyiv; [tt]the Department of Clinical and Laboratory Allergology and Immunology, National Medical Academy of Postgraduate Education, Kyiv; [uu]the Firestone Institute of Respiratory Health, Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton; [vv]the KEMRI-Wellcome Trust Research Programme (KWTRP), Kilifi; [ww]the Department of Allergology and Clinical Immunology, Research and Clinical Institute for Pediatrics named after Yuri Veltischev at the Pirogov Russian National Research Medical University of the Russian Ministry of Health, Moscow; [xx]the OncoGen Center, County Clinical Emergency Hospital "Pius Branzeu," and University of Medicine and Pharmacy V Babes, Timisoara; [yy]the Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester; [zz]the Allergy Department, 2nd Pediatric Clinic, National Kapodistrian University of Athens, Athens; [aaa]the Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon; [bbb]the Department of Pediatrics, Nippon Medical School, Tokyo; [ccc]the Pulmonary Department and Karl Landsteiner Institute for Clinical and Experimental Pulmology, Hietzing Hospital, Vienna; [ddd]the Institute of Laboratory Medicine, Universities of Giessen and Marburg Lung Center (UGMLC), Philipps University Marburg, German Center for Lung Research (DZL) Marburg, Marburg; [eee]the Asthma, Allergy and Immune Dysfunction Clinic, Twin Palms Medical Centre, Harare; [fff]the Department of Pathology, Medical School, National University of Science and Technology, Bulawayo; [ggg]Univ. Grenoble Alpes, Inserm, CNRS, Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health, IAB, Grenoble; [hhh]the Department of Allergology and Immunology, Rostov Medical University, Rostov; [iii]the Department of Allergy and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing; [jjj]the Department of Respiratory Diseases and Respiratory Allergy in Children, Institute of Pediatrics, Obstetrics and Gynecology, National Academy of Medical Sciences, Kyiv; [kkk]the Department of Paediatrics, National University of Singapore, Singapore; [lll]the Division of Immunology and Allergy, Department of Medicine, Karolinska Institutet and University Hospital, Stockholm; [mmm]the Center of Allergology and Clinical Immunology, Regional Clinical Hospital, Khabarovsk; [nnn]Dr. von Hauner Children's Hospital, Ludwig Maximilian University Munich, Munich; [ooo]the Institute of Asthma and Allergy Prevention, Helmholtz Centre Munich, Munich; [ppp]the German Centre for Lung Research; [qqq]the Center for Allergy and Clinical Immunology Research (ACIR), Department of Pediatrics, College of Medicine, National Cheng Kung University Hospital, Tainan; [rrr]the Department of Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong; [sss]the Department of Phtihisiatry and Pulmonology, Shupyk National Medical Academy of Postgraduate Education, Kyiv; [ttt]the University Clinic of Pulmonary and Allergic Diseases Golnik, Golnik; [uuu]the Faculty of Medicine, University of Ljubljana, Ljubljana; [vvv]the Division of Immunology and Allergy, Department of Medicine, Solna, Karolinska Institutet, Stockholm; and [www]Karl Landsteiner University, Krems.

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Corresponding author: Rudolf Valenta, MD, PhD, Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Waehringer Guertel 18-20, 3Q, 1090 Vienna, Austria. E-mail: rudolf.valenta@meduniwien.ac.at.

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Abbreviations used
GINA: Global Initiative for Asthma
RV: Rhinovirus

Asthma is a health problem of increasing importance, affecting more than 300 million people worldwide.[1] It is estimated that asthma contributes to approximately 0.4 million deaths every year and the mortality might be even increased in high-risk patients.[2,3] The number of disability-adjusted life-years due to asthma is approximately 23 million per year, and asthma thus accounts for approximately 1% of all disability-adjusted life-years lost.[1] A considerable proportion of the asthma burden is attributed to acute exacerbations, which are associated with high morbidity and can lead to death. Acute exacerbations of asthma are an enormous problem to both adults and children, and account for approximately 50% of asthma health care costs.[4] The rising prevalence of asthma and its accompanying health care costs are therefore major health and socioeconomic concerns.[5]

Patients suffering from asthma are often treated according to management strategies suggested by the Global Initiative for Asthma (GINA), which are regularly revised.[1] GINA defines asthma as "a heterogeneous disease usually characterized by chronic airway inflammation with a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitations." GINA is useful because it advocates management of asthma and respiratory disease according to published "good quality" evidence; however, suggested treatment options are limited to few drugs with little recommendations regarding the use of new biologics and other treatment options such as allergen-specific immunotherapy.[6,7]

Furthermore, GINA does not discriminate asthma according to the underlying trigger factors, which most certainly contribute to the phenotypic heterogeneity of asthma. Allergen exposure is a major asthma trigger factor for patients suffering from IgE-associated allergy.[8,9] Likewise, viral respiratory infections, particularly those caused by rhinoviruses (RVs), represent frequent triggers for acute asthma exacerbations in allergic as well as in nonallergic subjects.[10-12]

Recently, new biomarkers have been developed for the diagnosis of specific IgE sensitization toward a large variety of individual allergen molecules and for the detection of RV strain–specific IgG antibody responses.

CHIPS CONTAINING MICROARRAYED ALLERGEN MOLECULES OR PEPTIDES DERIVED FROM A COMPREHENSIVE PANEL OF RV STRAINS FOR SEROLOGY

Within 2 European Union–funded research projects, that is, MeDALL (https://cordis.europa.eu/project/rcn/96850/factsheet/en) and PreDicta (https://cordis.europa.eu/project/rcn/96868/factsheet/en), 2 multiplex assays have been developed on the basis of chips containing more than 170 different allergen molecules from various allergen sources[13] and microarrayed peptides from the VP1 coat proteins of the most common RV strains.[14] The MeDALL allergen chip measures IgE antibodies specific for a comprehensive panel of allergen molecules comprising a spectrum of the most common allergen sources, including all important respiratory allergen molecules such as the major house-dust mite allergens, animal-derived allergens, pollen allergens, and mould allergens. The allergen chip was shown to be more sensitive than current forms of skin prick testing and allergen extract–based IgE serology to identify subjects with specific IgE sensitizations[13,15] and most importantly, allowed precise identification of IgE sensitization to culprit allergen molecules for each individual patient. IgE testing with the allergen chip thus discriminates subjects with and without IgE sensitization. The analysis of IgE sensitizations against more than 170 allergen molecules can be performed with extremely low volumes of serum (ie, ~35 μL), which is particularly useful for an early detection of IgE sensitization in small children when limited amounts of blood is available (Fig 1, left part).[13]

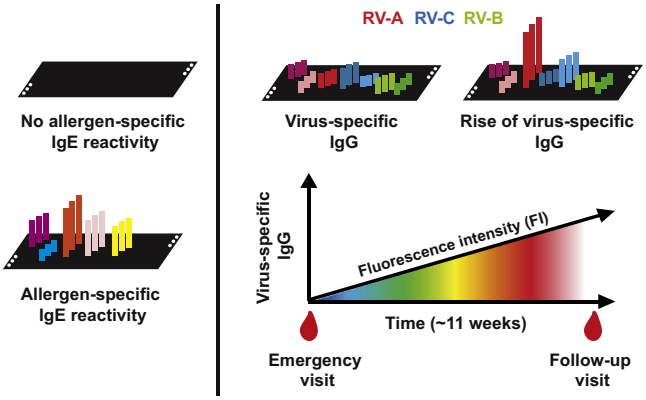

FIG 1. Chips containing a panel of microarrayed allergen molecules covering the most common allergen sources allow to measure IgE sensitization against each of the individual allergen molecules and thus of the culprit sensitizing allergens *(left).* Chips containing microarrayed peptides derived from the VP1 coat proteins of representative panels of RV-A, RV-B, and RV-C strains are useful for measuring RV-strain–specific IgG levels, cumulative strain–specific IgG levels, and increases in strain-specific IgG levels that occur some weeks after acute exacerbations of virus-triggered wheeze *(right).*

A further recent development is a chip containing peptides from the VP1 capsid proteins of panels of RV-A, RV-B, and RV-C strains, which can be used to measure strain-specific antibody responses in serum samples.[14] Cumulative levels of RV strain–specific antibody levels were associated with the severity of asthma-related symptoms in preschool children as recently demonstrated.[16] Furthermore, preschool children attending an emergency unit with acute exacerbations of wheeze showed strain-specific increases in virus-specific IgG antibodies in their follow-up serum samples obtained approximately 11 weeks later (Fig 1, right), suggesting that this increase is indicative of a wheeze attack triggered by a respiratory infection with certain RV strains. This assumption is corroborated by the observation that experimental infection with RV induced strain-specific increases in IgG antibody levels that were associated with the severity of RV-induced asthma in the tested subjects.[17] Thus, the chip containing microarrayed peptides from the most common RV strains seems to discriminate between infections caused by RV strains from the 3 groups A, B, and C, and species-specific levels of antibodies and their increases in the course of infection were shown to be associated with the severity of respiratory symptoms.[14,16] Using this RV chip we

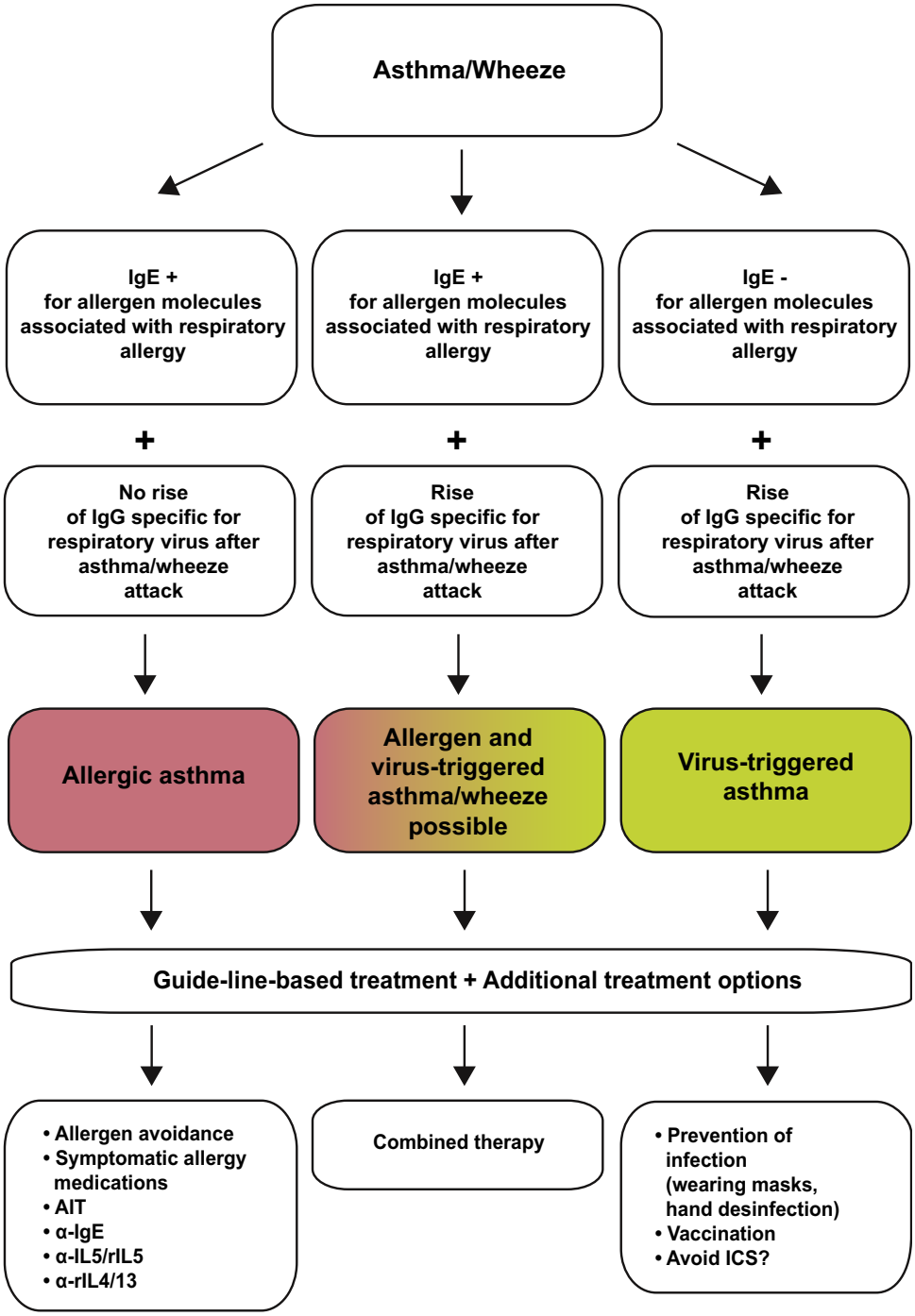

FIG 2. How the identification of allergens and respiratory virus infections as triggers factors of asthma and wheeze could lead to personalization of asthma treatment by adding treatment options to guideline-based therapy. *AIT,* Allergen immunotherapy; *ICS,* inhaled corticosteroid.

were previously able to identify species-specific antibody responses to RV-C–derived peptides, a species that has been difficult to propagate.[18] For the latter reason, we also know less about pathogenic differences between RV-A and RV-C strains in the etiology of asthma exacerbations because no infection models for RV-C are available.

THE POSSIBLE CLINICAL UTILITY OF MULTIPLEX SERUM-BASED ASSAYS FOR DISCRIMINATION OF ASTHMA TRIGGERED BY ALLERGENS OR VIRAL INFECTIONS

We would argue that the new, multiplex serum assays allow determination whether IgE reactivity against important

respiratory allergen molecules (Fig 1, left) or respiratory viral infections as evidenced by increases in virus-specific IgG (Fig 1, right) are trigger factors for an individual's asthma exacerbation. Data obtained in longitudinal birth cohorts and in studies of preschool children suffering from exacerbations of wheeze indicate that respiratory viral infections may be important trigger factors before relevant IgE sensitization to aeroallergens has occurred.[19,20] However, it has been found that early multiple allergic sensitization in the first years of life is an important predictor of asthma.[21-23] Thus, the importance of respiratory virus infections and allergen exposure for triggering asthma seems to vary by age. Furthermore, each of the 2 forms of asthma (ie, viral- and allergen-triggered asthma) may occur independently or in combination in the same individual.

It is, therefore, of great importance to identify early on high-risk children who are likely to develop persistent asthma later on in life.[24] It is estimated that approximately one-third of infants and toddlers who wheeze in the first 3 years of life continue to wheeze after the age of 3 years.[25] Although most children with viral-induced wheeze lose their respiratory symptoms in their early school age, have normal spirometry, and are more commonly nonatopic, they are usually less responsive to steroid treatment.[21,26] In contrast, children who become sensitized to common aeroallergens are more likely to retain their symptoms and have reduced lung function at school age.[25]

Although there is little doubt that exposure to both allergens and viral infections can induce asthma exacerbations, there is very little information regarding their interaction. It has proven to be very difficult to document personal allergen exposure leading to an exacerbation of asthma and perhaps this is the reason why very few reports document the interaction between naturally acquired viral infections and allergen exposure in asthma exacerbations. Green et al[27] provided evidence for synergy between viral infections and allergen exposure. In their case-controlled study, the risk of being admitted to hospital was considerably increased by exposure to high levels of allergen and concurrent viral infection. Another study reported that high titers of IgE antibodies to dust mite allergen were common and significantly increased the risk for acute wheezing provoked by RV among children with asthma.[28] However, regardless of the sequence of exposure to allergen and viral infection, both stimuli have been shown to affect the subsequent response to the other.[29]

In fact, allergic asthma is a classical type 2 (T2)-associated disease, whereas studies of the natural antibody response to RV indicate that RV infections are dominated by IgG_1 and IgA antibody responses and therefore are rather reminiscent of a type 1 type of immunity.[30] It is thus quite tempting to speculate that T2 asthma that is characterized by eosinophilia may be rather due to T2-dependent allergen-specific IgE sensitization, whereas asthma triggered only by certain respiratory virus infections (ie, without concomitant allergic sensitization) such as RV may belong to the T2-low or non-T2 asthma.[31] In addition, other trigger factors such as pollution, exercise, stress, and obesity may be important in the different phenotypes of asthma.

The availability of molecular multiallergen tests and chips containing peptides and antigens from important respiratory viruses provides the possibility to assess recent or past acquisition of respiratory viral infection and IgE sensitization to important respiratory allergens as trigger factors for asthma and to investigate how they are related to T2, T2-low, and non-T2 asthma .[31] These additional biomarkers may eventually allow us to develop a more refined asthma classification. Certainly, these biomarkers will inform whether the allergic sensitization, respiratory viral infection, or both play an important role in triggering asthma (Fig 2). First data indeed suggest that chip-based serological testing for RV infections may be more sensitive and specific than recording of upper respiratory tract symptoms and nucleic acid–based testing for RV infections often used in hospitalized patients to assume that asthma is triggered by RV infections.[14]

Based on such information, different forms of individualized treatment can be considered in addition to GINA-based therapy (Fig 2). For example, the identification of certain allergens as trigger factors may provide a rationale for allergen avoidance measures[32] and molecular approaches for allergen-specific immunotherapy.[33] Likewise, patients with asthma with IgE sensitization to important respiratory allergens may be particularly responsive to IgE-targeting treatment strategies such as anti-IgE or selective IgE immunoadsorption.[34] Furthermore, new biological treatments such as anti-T2 cytokine-based treatments may be very effective in patients suffering from severe asthma.[26,31]

However, one may consider measures to prevent viral infections such as wearing masks, hand disinfection, avoiding close contacts, and better ventilation of indoor environments to preclude virus-triggered asthma.[35,36] Vaccination against respiratory viruses responsible for virus-triggered asthma, although currently not an option, may be another option in the future. Furthermore, in the case that asthma triggered by respiratory virus infections indeed resembles a non-T2 phenotype, the use of corticosteroids may be less effective and/or not recommended. In this context, it is of note that some of the new corticosteroids do not seem to protect against barrier damage caused by RV infections.[37]

For patients suffering from mixed forms with evidence for allergens and virus infections as asthma triggers, one may try to separate out "hyperresponders" to allergens or virus infections. It is possible that atopic children with moderate to severe asthma triggered by RV infections may turn out to be better candidates for a vaccine targeting RV. Although these children are currently for treatment with biologic medications (eg, omalizumab and dupilumab), these medications are at present costly, there are some poor responders, and, once started, clinicians face the challenge of deciding when to stop these treatments, which may become easier if vaccines become available.

SUMMARY

It is possible that new serological multiplex tests may improve clinical outcome by determination of allergen- and virus-triggered asthma, enabling classification of patients with asthma according to underlying trigger factors, which may help them to benefit from personalized forms of treatment while taking into account established GINA-based treatment.

Clinical trials to test whether personalization of asthma treatment based on serological identification of possible trigger factors can improve current asthma management guidelines are warranted.

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