World Allergy Forum:
Global Trends in Allergen Immunotherapy

Mario Sanchez Borges Memorial Lectures

Bryan L. Martin, DO, FACAAI
President-Elect, World Allergy Organization
Past-President, ACAAI
Professor, Medicine and Pediatrics
Chief, Allergy Immunology Division
The Ohio State University

Mario Sánchez Borges Memorial Lectures
WAO Past President: 2016-2017
World Allergy Forum

Global Trends in Allergen Immunotherapy

Mario Sánchez Borges Memorial Lectures

WELCOME

Sunday, 7 November 2021
10:00 to 11:30 AM
ACAAI Annual Meeting 2021 New Orleans
Dedication

WAO dedicates today’s World Allergy Forum
to the memory of Professor Mario Sánchez Borges

Mario Sánchez Borges, MD
WAO Past President 2016-2017
Respected Friend and Colleague

A Tribute to Mario Sanchez Borges

It is with extreme sadness that we must report the passing of Mario Sanchez Borges, a Past President and current Councillor of the World Allergy Organization (WAO). Mario was a prominent figure in International Allergy and Immunology and his scholarly and academic achievements were in addition to his contributions to our discipline and profession.

Mario was a wonderful person and colleague. A great friend and collaborator with a large capacity for empathy and support. His personal support was supplemented by a great sense of humor and understanding that anything could be accomplished by working together. A superb physician and an outstanding translational scientist, Mario made contributions in these areas continuously. No one in Allergy conducted him or herself with the integrity of Mario Sanchez Borges in a variety of circumstances. Mario worked very hard on all his assignments and often finished his superb work ahead of schedule.

Mario attended medical school in Caracas, Venezuela and trained in Allergy and Immunology there. He also did training in basic Allergy Immunology at Tokyo University with Professor Tomio Tada. Mario led an active career in his national allergy society and in the Latin American region. Over the past 16 years Mario has had a very productive time with WAO serving as President for 2016-2017 and currently as Councillor.

On a personal note we have all had the honor and pleasure of working closely with Mario. His professional attitude made him a reliable partner of great integrity. But most important his sense of humor and supportive actions made his humanity an even more precious center for a most valued friendship. His presence will be missed as we all hoped for many years of continued friendship.

Lanny J. Rosenwasser, Ignacio J. Anzotegui & Motohiro Ebisawa
on behalf of the WAO Board of Directors
Dr. Mario Sanchez Borges and his wife, Maria

Dr. Borges was a scholar

- Over 350 published manuscripts
- 22,910 citations noted
Mario was a friend to the profession
When work was over, it was time to have fun.

Shown with Dr. Borges

- Dr. Bryan Martin & Dr. Dana Wallace (ACAAI)
- Dr. Ignacio Ansotegui (Spain)
- Dr. Walter Canonica (Italy) (WAO)
World Allergy Organization (WAO)

The World Allergy Organization (WAO) is an international umbrella organization whose members consist of 104 regional and national allergy and clinical immunology societies from around the world.

Our mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training, as a worldwide alliance of allergy and clinical immunology societies.

World Allergy Forum

The World Allergy Forum (WAF) is the longest-running educational program of WAO.

It was developed by international advisory panels, to provide up-to-the-minute presentations on scientific and clinical developments in the field of allergy/immunology.

WAF symposia are held at major international allergy meetings.
World Allergy Organization (WAO)

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World Allergy Organization & BSACI

2022 UK Conference
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FOOD AND RESPIRATORY ALLERGIES
18-20 MAY 2023 🌺 KONA, HAWAI’I

www.worldallergy.org/HawaiiSymposium
All of you are members of WAO!

All active members of WAO member societies are individual members of WAO.

Thank you for being here today.

www.WorldAllergy.org
Global Trends in Allergen Immunotherapy

Chairpersons
WAO: Bryan Martin, DO | ACAAI: Luz Fonacier, MD

Epicutaneous Immunotherapy for Food Allergy
DAVID M. FLEISCHER, MD
University of Colorado School of Medicine
Aurora, Colorado, United States

Efficacy and Safety of Polymerized Extracts in Allergen Immunotherapy
IGNACIO J. ANSOTEGUI, MD, PHD
Hospital Quironsalud Bizkaia
Bilbao, Spain

Controversies in Sublingual Immunotherapy
G. WALTER CANONICA, MD, PHD
Humanitas University
Humanitas Research Hospital IRCCS
Milan, Italy
Immunotherapy, the paradigm of Personalized Medicine

Prof. Giorgio Walter Canonica
FERS, FACAAI, FAAAAI, FEACCI
GINA Advocate
Editor in Chief: Current Opinion Allergy & Clinical Immunology

Personalized Medicine Asthma & Allergy Clinic

Canonica G.W. Disclosure of Interests
GWC reports having received in the last 3 years research grants as well as lecture or advisory board fees from:

• A.Menarini
• Alk-Abello’
• Allergy Therapeutics
• Anallergo
• AstraZeneca-Medimmune
• Boehringer Ingelheim
• Chiesi Farmaceutici
• Danone
• Faes
• Genentech
• Guidotti-Malesci
• Glaxo Smith Kline
• Hal Allergy
• Merck Sharp & Dome
• Mundipharma
• Novartis
• Orion
• Sanofi-Aventis
• Sanofi Genzyme/Regeneron
• Stallergenes
• UCB Pharma
• Uriach Pharma
• Teva
• Thermo Fisher
• Valeas
• ViforPharma
Commemorating 110 Years of Allergen Immunotherapy

FIGURE 1. One hundred ten years of allergen immunotherapy (modified from Durham and Leung®): many innovations have fueled clinical development and regulatory guidance. This has led to an increased body of evidence, systematic reviews, and guidelines for both subcutaneous (SCIT) and sublingual (SLIT) applications of allergen immunotherapy (AIT). In 2020, during the global coronavirus SARS-CoV-2 (COVID-19) pandemic, special emphasis was put on AIT as the only disease-modifying option altering the immunological mechanisms. EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; FDA, Food and Drug Administration; PEI, Paul-Ehrlich-Institut.

Pfaar et al. JACIP 2021

FIGURE 3. Routes of administration in allergen immunotherapy (AIT) (A) and number of papers indexed in PubMed for AIT, oral immunotherapy (OIT), intralymphatic immunotherapy (ILIT), epicutaneous immunotherapy (EPIT) (B). The figure indicates the time frames in which double-blind placebo-controlled trials (DBPCCTs) were performed for the different application routes and their current usage status. Numbers in (B) are recorded since 1946. LBIT, local bronchial immunotherapy; LNT, local nasal immunotherapy; SCIT, subcutaneous AIT; SLIT, sublingual AIT.

Pfaar et al. JACIP 2021
ARIA-EAACI care pathways for allergen immunotherapy in respiratory allergy

FIGURE 1 Countries with Pocket Guide members

Bousquet et al Allergy 2021

FIGURE 4 Algorithm for AIT in asthma

Bousquet et al Allergy 2021
3.1 Precision medicine in the indication of AIT

1. **Precise diagnosis** with history, skin prick tests and/or specific IgE and, if applicable, component-resolved in vitro testing. In some cases, where the above-mentioned diagnostic tools do not allow for precise diagnosis, allergen provocation testing (nasal, ocular and, in some cases, bronchial) may be needed.

2. **Proven indications**: Allergic rhinitis, conjunctivitis and/or asthma.

**Bousquet et al Allergy 2021**
Specific immunotherapy

- **Molecular-based allergy (MA) diagnostics represents a useful tool to distinguish genuine sensitisations from cross-reactions in poly-sensitized patients**. When traditional diagnostic tests and clinical history are unable to identify the relevant allergen(s) for specific immunotherapy (SIT).

- **Given that SIT is an expensive treatment typically used over longer periods of time (3 to 5 years), correct diagnosis, selection of truly eligible patients, and identification of primary sensitizing allergen(s) are important for optimal and cost-effective patient management.**

AlIT-Allergen ImmunoTherapy

Molecular diagnostics may also improve the selection of both patients and specific allergens for specific immunotherapy (SIT) for inhalant allergies (e.g., for pollen) [11,12] and hymenoptera venom allergy [13,14]. An ever
Patients most likely to benefit from molecular-based allergy diagnostics

- Molecular-based allergy (MA) diagnosis is most useful for selection of SIT, evaluation of cross-reactivity, and assessment of severity of reaction associated with various allergens.

In poly-sensitized patients, the most relevant sensitizing allergens for which SIT should be prescribed can be more clearly identified with MA diagnostics. A recent study reported that MA diagnostics modified the prescription of SIT compared to SPT in more than 50% of patients [11], suggesting that poly-sensitized patients are at risk of incorrect SIT prescription.


Precision allergy molecular diagnostic applications (PAMD®)
Possibly, in the past, the concept of AIT as Precision Treatment was not properly considered or emphasized, but it was there, and still is upfront.

"it was there, but we didn’t think about"

GWC 2015

Passalacqua & Canonica C.M.A. 2015
**Canonica et al WAO J. 2015**

**Allergen Immunotherapy (AIT): a prototype of Precision Medicine**

**Molecular mechanism:**
IgE, arming effector cells, binds allergen/component → mediator release & symptoms

**Diagnostic Tool:**
IgE to causal allergen/component detection

**Treatment Blocking**
the Molecular Mechanism

**AIT - Allergen Immunotherapy**
(SCIT-SLIT)

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**Hamburg & Collins, NEJM 2010 [22]**

Identification of Molecular Mechanism of disease

**Diagnostic Tool**
for the Molecular Mechanism

**Treatment Blocking**
the Molecular Mechanism

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**Canonica et al. WAO J.2015 [18]**

Passalacqua & Canonica, CMA 2015 [23]

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**Canonica et al. Curr. Opin. Pulm. Med. 2015**

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**AIT as PRECISION THERAPY**
Personalized Medicine

is focused on the PATIENT-PERSON not just on the mechanism
At present 2021
58 Inhalers in Italy

**Importance of inhaler devices in the management of airway disease**

Respiratory medicine 2007

<table>
<thead>
<tr>
<th>Error Description</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous pMDI experience (n = 1.133)</td>
<td></td>
</tr>
<tr>
<td>Action before inspiration</td>
<td>18</td>
</tr>
<tr>
<td>Action at end of inspiration</td>
<td>17</td>
</tr>
<tr>
<td>Action caused by stop of inspiration</td>
<td>25</td>
</tr>
<tr>
<td>Actuated in mouth but inhaled through nose</td>
<td>14</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>86(9%)</td>
</tr>
<tr>
<td>Previous pMDI experience (n = 113)</td>
<td></td>
</tr>
<tr>
<td>Action before inspiration</td>
<td>1</td>
</tr>
<tr>
<td>Action before inspiration</td>
<td>35</td>
</tr>
<tr>
<td>Action at end of inspiration</td>
<td>38</td>
</tr>
<tr>
<td>Action caused by stop of inspiration</td>
<td>27</td>
</tr>
<tr>
<td>Actuated in mouth but inhaled through nose</td>
<td>12</td>
</tr>
<tr>
<td>Multiple actuations—same inhalation</td>
<td>17</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
</tr>
</tbody>
</table>
| Total                                                   | 135(113)%          

✓ Only 21% of patients were able to correctly use a pMDI after reading the package insert and

✓ Only 52% of patients correctly used a pMDI after receiving instruction
Multiple inhalers confuse asthma patients


ABSTRACT: This study investigated the influence of the use of different types of inhalers on the adequacy of inhalation technique among adult asthmatics. Three hypotheses were tested: first, patients using only one type of inhaler will demonstrate adequate inhalation technique more often than those with two or more types. Secondly, patients

van der Palen et al, ERJ 1999

The Need for Humanomics in the Era of Genomics and the Challenge of Chronic Disease Management

J. Mark FitzGerald, MD
Iraj Poureslami, PhD
Vancouver, BC, Canada

VIEWPOINT

Personomics

It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.

Sir William Osler

JAMA Internal Medicine 2015

DEBATE
Implementing shared decision-making: consider all the consequences
Glyn Elwyn1, Dominic L. Fosch2,3 and Sarah Kobrin4

Conclusion: We suggest that a broader conceptualization and measurement of shared decision-making would provide a more substantive evidence base to guide implementation. We outline a framework which illustrates a hypothesized set of proximal, distal, and distant consequences that might occur if collaboration and deliberation could be achieved routinely, proposing that well-informed preference-based patient decisions might lead to safer, more cost-effective healthcare, which in turn might result in reduced utilization rates and improved health outcomes.

Elwyn et al, 2016
PERSONALIZED MEDICINE & AIT GUIDELINES

EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma

Agache et al. Allergy 2019
1. Diagnose (symptoms, lung function, AHR, biomarkers, etc.)
   - Atopic status (skin prick test, serum specific IgE)
   - Component-resolved diagnosis
   - Co-morbidities: atopic dermatitis, food allergy, AR

2. Characterise the allergic phenotype
   - History ± HDM provocation test

3. Evaluate the impact of allergic sensitisation on asthma symptoms and control
   - Asthma with HDM sensitisation
   - HDM-driven allergic asthma
     - Regular controller treatment
     - Consider HDM AIT added to regular controller treatment

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10.1 Conclusion. Key points

1. Patients with HDM-driven allergic asthma not adequately controlled on available pharmacotherapy present an unmet health need.
2. AIT targets the underlying mechanisms in allergic asthma by modifying the immunological response to allergen toward tolerance.
3. HDM AIT may add to the anti-inflammatory action of ICS to promote asthma control and decrease the risk of exacerbations.
4. Success of HDM AIT in HDM-driven allergic asthma is largely dependent on proper selection of patients with HDM sensitization and symptoms driven by specific allergen exposure plus the use of allergen extracts of proven efficacy.
5. To date, only AIT with HDM SLIT-tablet has been demonstrated to show robust effects in adults on critical end points (exacerbations, asthma control, and safety).
6. AIT should only be initiated and monitored by healthcare professionals with the appropriate competencies which will require an investment in training.
Incorvaia et al. 2020

**Personalized medicine for allergy treatment: Allergen immunotherapy still a unique and unmatched model**

Incorvaia et al. 2020

**ALGORITHM to AIT Prescription**

Incorvaia et al. 2020
Figure 2 – Tools for personalized Allergen Immunotherapy

Validated tools for AIT
- Clinical history
- Skin tests with allergen extracts
- Serum-specific IgE
- Component-resolved diagnosis
- CAP-Inhibition (limited)

Tools still to be validated for AIT
- Basophil activation test
- Nasal cytology
- Nasal challenge with the suspected allergen

Tools of future applications
- Treatable traits (genetic, phenotypic, psychosocial features)
- Omics (proteomics, epigenomics, metabolomics, breathomics)

Incorvaia et al. Allergy 2020
A WAO – ARIA – GA²LEN consensus document on molecular-based allergy diagnosis (PAMD@): Update 2020


**Precision allergy molecular diagnostic applications (PAMD@)**

**MOLECULAR DIAGNOSIS AND ALLERGEN IMMUNOTHERAPY**

PAMD@ represents a useful tool to distinguish clinically relevant and/or primary sensitizations from cross-sensitization in polysensitized patients in cases where traditional diagnostic tests and clinical history are unable to identify the relevant allergen(s) that should be used for AIT. AIT is an
House dust mites

The presence of IgE to both Der p 2 and Der p 1 has highly significant predictive value for immediate-type asthma. In a birth cohort study of 1184 subjects in Italy, a combined sensitization to Der p 1 and Der p 2 represented the highest risk factor for asthma development, independent of age. Others have reported the specific impact of Der p 2 and Der f 2 on severe asthma. Cysteine proteases, such as Der p 1 and papain, may have a percutaneous sensitization capacity in addition to the described capacity to disrupt bronchial epithelial barriers. Der p 23 is a major allergen associated with asthma in both pediatric and adult populations. The recently identified Der p 11 (a non-fecal allergen from Dermatophagoides pteronyssinus) seems to be a useful serological marker for the identification of a subgroup of HDM-allergic patients suffering from atopic dermatitis. The development of HDM allergen sensitization during life (the so-called allergen march) has been studied at a molecular level with their relationships with symptons.
3. The molecular allergology approach

The molecular allergology approach in allergic asthma allows (Fig. 3):

- A better understanding of disease mechanisms (molecular characterisation of allergens relevant to asthma, genetics and epigenetics studies, animal models, single cell analysis, CRISPR/Cas9 targeted intervention, T cell and receptor editing, novel mediators)
- Precise diagnosis through the description of the molecular allergen sensitisation profile
- Optimal selection of responders to the targeted treatment, either with AIT, or with biologics
- Novel approaches to allergic asthma (adoptive cell therapies)
Component-Resolved Diagnosis to Optimize Allergen-Specific Immunotherapy in the Mediterranean Area

R. Valenta, T. Twaroch, I. Swoboda

Christian Doppler Laboratory for Allergy Research, Division of Immunopathology, Department of Pathophysiology, Center for Physiology and Pathophysiology, Medical University of Vienna, Austria

Asthma Research and Practice

Potential of molecular based diagnostics and its impact on allergen immunotherapy

Giovanni Melioli, Eleonora San, Maria Angela Cirello, and Giovanni Passalacqua

2007

2016
Association between component-resolved diagnosis of house dust mite and efficacy of allergen immunotherapy in allergic rhinitis patients

In summary, this study has provided preliminary information of the allergenic profiles of major HDM components; especially Der p 1, Der p 2, Der p 23, Der f 1 and Der f 2; at baseline and over a course of 52-week AIT in patients with HDM-induced AR. Furthermore, Der p 1 appears to be the most clinically relevant allergenic component for effective AIT, and the ratio of Der p 1-sIgE/Der p 1-sIgG4 levels may be useful as a biomarker for predicting the clinical responses of AIT.

The Role of Aeroallergen Sensitization Testing in Asthma Management

Finally, an area of future study is to define whether molecular component diagnostics will improve the accuracy of identifying clinically significant allergy for asthmatics as well as better guide therapeutic choices (ie, component-directed AIT).
Coordinated IgG2 and IgE responses as a marker of allergen immunotherapy efficacy

Véronique Bordas-Le Floch1 | Nathalie Berjont1 | Thierry Batard1

Niurama Varese2,3 | Robyn E. O’Hehir2,3 | Walter G Canonica4,5

Menno C. van Zelm2,3 | Laurent Mascalchi6

Bordas-Le Floch et al Allergy 2021

GRAPHICAL ABSTRACT

This study assesses humoral responses in HDM-allergic individuals before and after 1-year HDM tablet sublingual AIT. Individuals suffering from HDM allergy exhibit an increase in serum HDM-specific IgG2 following 1-year AIT. Correlations observed between changes in IgG2 and IgE antibody levels highlight coordinated humoral responses only in high responders during AIT.
Molecular allergology and its impact in specific allergy diagnosis and therapy

Domingo Barber1,2 | Araceli Díaz-Perales1,3 | Maria M. Escribés1,2 | Jörg Kleine-Tebbe4 | Paolo M. Matricardi5 | Markus Ollert6,7 | Alexandra F. Santos1,2,9,10,11 | Joaquín Sastré1,2

2021

Major milestones:
- IgE Discovery (1948)
- First commercial reagents for specific IgE (1972)
- Knowledge and Characterization of the most relevant allergens (1985–2005)
- Development of multiplex allergens: 1999
- Handbook of Molecular Allergology: 2016
- Progressive use in clinical practice of CPT: 2010–2021
- First AIT product registered following Pharmaceutical development guidelines: 2007
- First OIT for peanut allergy registered: 2020

Future research perspectives:
- Affinity and avidity need to be explored in IgE response to allergens
- T-cell reactivity to allergens is a critical parameter
- Combination of new biologics and AIT and associated diagnosis will open new intervention strategies
- New regulation of in vitro diagnostics will increase the quality of CPT, but might limit innovation and available molecules

Table 1: Characteristics and significance of pollens, vegetables, fruits, and other allergens available for CPT and relevant for AIT reactions.

<table>
<thead>
<tr>
<th>Source</th>
<th>Allergens</th>
<th>Specificity (%)</th>
<th>Available for treatment</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollen</td>
<td>Phl p 1</td>
<td>&gt;90%</td>
<td>S, M</td>
<td>IgE positive in different plant parts, major allergen and causes allergic sensitisation.</td>
</tr>
<tr>
<td></td>
<td>Phl p 3</td>
<td>&gt;60%</td>
<td>S, M</td>
<td>Unknown function, most abundant pollen protein</td>
</tr>
<tr>
<td></td>
<td>Phl p 7</td>
<td>&lt;20%</td>
<td>S, M</td>
<td>Fert in pollen, calcium binding</td>
</tr>
<tr>
<td></td>
<td>Phl p 10</td>
<td>5–10%</td>
<td>S, M</td>
<td>For allergy to pollen, structural protein</td>
</tr>
<tr>
<td>Beet</td>
<td>Bch b 1</td>
<td>&gt;40%</td>
<td>S, M</td>
<td>For allergens (сходencias) regulatory protein, highly expressed in case of betel thios</td>
</tr>
<tr>
<td>Oat</td>
<td>Oal c 1</td>
<td>&gt;90%</td>
<td>S, M</td>
<td>Unknown function</td>
</tr>
<tr>
<td>Oats</td>
<td>Oat a 7</td>
<td>30–40%</td>
<td>S, M</td>
<td>Maize, rice allergens, disease severity marker</td>
</tr>
<tr>
<td>Oils</td>
<td>Oen a 9</td>
<td>5–10%</td>
<td>S, M</td>
<td>Common major allergen, highly variable in different oil cultivars</td>
</tr>
<tr>
<td>Rye</td>
<td>Sec a 1</td>
<td>&gt;50%</td>
<td>S, M</td>
<td>Fert with birch tree</td>
</tr>
<tr>
<td>Freshwater</td>
<td>Phl g 1</td>
<td>&lt;20%</td>
<td>S, M</td>
<td>Invertebrate inhibitor</td>
</tr>
<tr>
<td>Astrocycla</td>
<td>Cop r 1</td>
<td>&gt;90%</td>
<td>S, M</td>
<td>Fert In hay, bee pollen, and more reactive to Cry s 1, non-cry1, and act 1 from mustard cake</td>
</tr>
<tr>
<td>English mustard</td>
<td>Plu p11</td>
<td>&gt;70%</td>
<td>S, M</td>
<td>Ole a 1 like, non-reactive</td>
</tr>
<tr>
<td>Artichoke</td>
<td>Car a 1</td>
<td>&gt;70%</td>
<td>S, M</td>
<td>Fert In artichoke</td>
</tr>
<tr>
<td>Rapeseed</td>
<td>Ali a 1</td>
<td>&gt;70%</td>
<td>S, M</td>
<td>Fert in rape seed</td>
</tr>
<tr>
<td>Parmesan</td>
<td>Pyg a 2</td>
<td>&gt;60%</td>
<td>S, M</td>
<td>Casein-like protein</td>
</tr>
</tbody>
</table>

Barber et al. Allergy 2021
Figure 1. Diagnostic algorithm and decision tree for AIT using CRD in Grass pollen allergy. Grass pollen allergy is one of the most studied allergy models. Major allergen sensitization is required before considering AIT. The combination of major allergens and pan-allergens provides the necessary tools for AIT decisions. Profilin allergy might be a contraindication only in severe food allergic patients, while double sensitization to both pan-allergens is associated to many years of disease evolution, poly-sensitization, and poor intervention outcome.

Barber et al. Allergy 2021

Figure 2. Diagnostic algorithm and decision tree for AIT using CRD in Olive pollen allergy. Olive pollen allergies are one of the most complex allergy models. Usually olive cultivars cover homogeneous areas and present acute differences in allergen pollen content. In dense pollen areas, patients are exposed to the highest pollen counts recorded. Through existing of complex profiles, marked by minor allergens sensitization, makes CRD a fundamental tool for patient management and AIT decisions.

Barber et al. Allergy 2021
**Figure 3** Diagnostic algorithm and decision tree forAIT using CRD in nsLTP mediated allergy. The existence of cross-reactivity between nsLTPs from Artemisia and Pistatius pollens makes CRD necessary. LTP immunotherapy with an enriched Pru p 3 can be considered in Countries with availability of this type of therapy.

Barber et al. Allergy 2021

**Figure 5** Diagnostic algorithm for in vitro diagnostics in epithelial allergy, and associated decision tree for AIT using CRD. The proposed algorithm discriminates between primary sensitization and cross-reactive sIgE response. Only patients sensitized to major allergens should be eligible for AIT.

Barber et al. Allergy 2021
KEY MESSAGE

To rely on correctly standardized and clinically documented AIT products, as well as to understand their limitations, is as important as correctly diagnosing patients.
Novel antibody cocktail targeting Bet v 1 rapidly and sustainably treats birch allergy symptoms in a phase 1 study

Philippe Gevaert, MD, PhD, a,b Jarno De Craecker, MD, a Natalie De Ruyck, MS, a Sylvie Rottey, MD, PhD, a,b Jan de Hoon, MD, PhD, a,b Peter W. Hellings, MD, a,b,c Bram Volckaert, MD, a,b Kristof Losneuck, MS, a Jamie M. Orense, PhD, a,b Amanda Atanasio, MS, a,b Mohamed A. Kamal, PhD, a,b Hisham Abdallah, PhD, a,b Vishal Kamat, PhD, a,b Robert Dingman, PhD, a,b Michelle Devaex, PhD, a,b Divya Ramesh, PhD, a,b Lorah Perlee, PhD, a,b Claire W. Wang, PhD, a,b David M. Weinreich, MD, a,b Gary Herman, MD, a,b George D. Yancopoulos, MD, PhD, a,b, and Meagan P. O’Brien, MD, a,b, Ghes, Leuven, and Antwerp, Belgium; Amsterdam, The Netherlands; and Tarrytown, NY

Conclusions: Single-dose REGN5713/14/15 was well tolerated and provided a rapid (1 week) and durable (2 months) reduction in allergic symptoms after birch allergen nasal allergen challenge, potentially offering a new paradigm for the treatment of birch allergy symptoms. (J Allergy Clin Immunol 2021;.)

Gevaert et al. JACI 2021

GRAPHICAL ABSTRACT

Novel antibody cocktail targeting Bet v 1 rapidly and sustainably treats birch allergy symptoms in a Phase 1 study

AUC, area under the curve; BAT, basophil activation test; Bet v 1, major birch tree allergen; FPIR, first-in-human; FEF25, first-patient first-in; L5, level 5 squares; NAC, nasal allergen challenge; PDC, provocation dose; SPT, skin prick test; TNKS, total nasal symptom score

Gevaert et al. JACI 2021
**Allergen immunotherapy and biologics in respiratory allergy: friends or foes?**

Malipiero et al. COACI 2021

**KEY POINTS**

- AIT is the only available causative treatment in allergy practice but its use requires long-term treatment and can be limited by a number of safety issues, particularly in high-risk clinical scenarios.

- Biologicals targeting type 2 inflammatory mechanisms, from IgE-allergen interaction to tissue recruitment of inflammatory cells, have been used to prevent severe allergic reactions and treat severe type 2 inflammatory diseases.

- The combination of biologicals and AIT has been already explored in clinical practice, with favorable results on safety endpoints but its role in increasing long-term efficacy of AIT should be further defined.

**ALLERGEN IMMUNOTHERAPY AND BIOLOGICALS COMBINATION TREATMENT**

**AIT effectiveness**
- Long-term tolerance induction
- Prevention of asthma and airway remodeling

**AIT adverse events**
- Rush immunotherapy
- High-risk patients

**Extend AIT indications**
- Severe asthma
- Uncontrolled occupational allergic diseases
- SLIT for allergic rhinitis/asthma in EoE patients

**Steroid-sparing effect**
- OCS use
- ICS step-down

**Malipiero et al. COACI 2021**
How to create a Sustainable New Scenario to reflect a change

PATIENTS SELECTIONS for Randomized Controlled Trials

Patients in Randomized Controlled Trials & in everyday Clinical Practice

- Patients selected in RCTs
- Patients in everyday Clinical Practice

Randomised controlled trial vs. real-world evidence

Efficacy x Adherence = Effectiveness

Efficacy is the effect under the perfect conditions.

Effectiveness is the effect in the real world.

RCTs: Efficacy
- Double-blind
- Double-dummy
- Strict inclusion criteria
- Defined exclusion criteria
- Adherence encouraged
- Frequent reviews
- Drugs provided to subjects

Clinical Effectiveness
- Open-label
- Broad population
  - Eligible patients with minimum exclusion criteria
- Comorbid included
- Set in normal care
- No extra review
- Drugs prescribed and picked up patients

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Real world evidence (RWE) – an introduction; how is it relevant for the medicines regulatory system?

London, EMA, April 2018

Hans-Georg Eichler
Senior Medical Officer
The importance of real-life research in respiratory medicine: a manifesto

endorsed by the International Primary Care Respiratory Group and the World Allergy Organization

10/18/2021

https://doi.org/10.1186/s13314-019-0256-9

Clinical and Translational Allergy

The REal Life EVIDence Assessment Tool (RELEnVANT): development of a novel quality assurance asset to rate observational comparative effectiveness research studies

Jonathan D. Campbell, Robert Perry, Nikolaos G. Papadopoulos, Jerry Krishnan, Guy Brusselle, Alison Chisholm, Leif Bjørmer, Michael Thomas, Eric van Ganse, Maarten van den Berge, Jennifer Quint, David Price and Nicolas Roche
Allergen immunotherapy: The growing role of observational and randomized trial “Real-World Evidence”

Giovanni Paoletti | Danilo DiBona | Derek K. Chu | Davide Firru | Enrico Heffler | Ioana Agache | Marek Jutel | Ludger Klimek | Oliver Pfaar | Ralph Mösges | Audrey Dunn Galvin | Jon Genuenit | Hans Jürgen Hoffmann | Giorgio Walter Canonica

Paoletti G., Di Bona D. et al. Allergy 2021

TABLE 1: The strengths of Clinical Trial compared to Real-world evidence

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Real-world evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range from proof of concept to registration studies</td>
<td>* No a priori exclusion of patient (e. smokers, elderly patients with comorbidities)</td>
</tr>
<tr>
<td>Robust protocol with control groups and randomized selection of treatment</td>
<td>Safety in a large group of patients and longer treatment period</td>
</tr>
<tr>
<td>Useful to define eligible patients</td>
<td>Effect on &quot;real&quot; patient effectiveness</td>
</tr>
<tr>
<td>Perusal of endpoint success</td>
<td>Revealed responder profile</td>
</tr>
<tr>
<td>First insight on test responders (secondary analysis)</td>
<td>Possible effect on comorbidities</td>
</tr>
</tbody>
</table>

Paoletti G., Di Bona D. et al. Allergy 2021

TABLE 2: The definition of the type of studies present in the proposed hierarchy of allergen immunotherapy real-world evidence

Pragmatic randomized controlled trial: Trials designed to evaluate the effectiveness of interventions in real-life routine practice conditions, opposite to explanatory trials that aim to test whether an intervention works under optimal situations.32

Registry real-world evidence: An organized system that uses observational methods to collect uniform data relative to real-world settings on specified outcomes in a population defined by a particular disease, condition, or exposure.41

Prospective database real-world evidence: A type of cohort study, where participants are enrolled into the study before they develop the disease or outcome in question in a real-world context.51

Retrospective multicenter database real-world evidence: is based on the use of an existing database to respond retrospectively to clinical questions.61

Retrospective multicenter real-world evidence: is a clinical trial conducted at more than one medical center or clinic where, in contrast to a prospective study, the outcome of interest has already occurred at the time the study is initiated.64

Expert experience/evidence: somebody who has a broad and deep competence in terms of knowledge, skill, and experience through practice and education in a particular field.
CRITICAL EVALUATION
of
REAL WORLD EVIDENCES
Quality standards in respiratory real-life effectiveness research: the REAl Life EVidence AssessmeNt Tool (RELEVANT): report from the Respiratory Effectiveness Group—European Academy of Allergy and Clinical Immunology Task Force

Nicolas Roche1, Jonathan D. Campbell2, Jerry A. Krishnan3, Guy Brusselle4, Alison Chisholm5, Leif Bjermer6, Mike Thomas7, Eric van Ganse8, Maarten van den Berge9, George Christoff10, Jennifer Quint11, Nikolaos G. Papadopoulos12 and David Price13

Table 3 Summary table of literature analysis, PICOT question 1: influence of adherence to ICS therapy on asthma outcomes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Statement</th>
<th>Type of data source</th>
<th>Final level of evidence (see Fig. 1)</th>
<th>Possible impact on clinical practice (TF opinion)</th>
<th>Similar evidence available from RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al.</td>
<td>Low adherence increases the risk of ED visits and oral steroid treatment</td>
<td>D-M</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Taegtmeyer et al.</td>
<td>Lower ACQ improvement associated with low adherence</td>
<td>PC-A</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Laforest et al.</td>
<td>Low adherence (MPR) associated with poorer control and more hospital contacts and oral steroid courses</td>
<td>PC-A</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Laforest et al.</td>
<td>Low adherence (MPR) increases the risk of oral steroid treatment and hospitalization</td>
<td>D-A</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sadatsafavi et al.</td>
<td>Risk of asthma-related hospitalization lower with ICS-containing regimen than LABA alone</td>
<td>D-M</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Risk of asthma-related hospitalization similar between ICS and LABA</td>
<td>D-M</td>
<td>Moderate</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td></td>
<td>Risk of asthma-related hospitalization increases when ICS treatment is irregular</td>
<td>D-M</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Friedman et al.</td>
<td>Adherence and SABA use are better with MF than FT DPIs, with no difference in other clinical outcomes</td>
<td>D-M</td>
<td>Moderate</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Campbell et al.</td>
<td>Shifting drug costs to patients decreases adherence and impairs asthma outcomes</td>
<td>D</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tari et al.</td>
<td>In adherent patients, ICS &gt; LTRA</td>
<td>D + S</td>
<td>Moderate (D), low (S)</td>
<td>Yes</td>
<td>In part (pragmatic RCT)</td>
</tr>
<tr>
<td></td>
<td>In non-adherent patients, ICS &gt; LTRA</td>
<td>D + S</td>
<td>Moderate (D), low (S)</td>
<td>Yes</td>
<td>In part (pragmatic RCT)</td>
</tr>
</tbody>
</table>

SABA short-acting beta agonist, LABA long-acting beta2 agonist, ICS inhaled corticosteroid, LTRA leukotriene-receptor antagonist, MF mometasone furoate, FP fluticasone propionate, D database, PC prospective cohort, S survey, M matched, A adjusted, RCT randomized controlled trial, MPR medication possession ratio, ED emergency department, TFQ asthma control questionnaire, TF task force

* Opposite finding regarding the risk of severe asthma exacerbations in several trials.
Allergen immunotherapy for respiratory allergy: Quality appraisal of observational comparative effectiveness studies using the REal Life Evidence Assessment Tool. An EAACI methodology committee analysis

DiBona et al Clin.Trans.Allergy 2021

RELEVANT quality is defined as fulfilment of all 11 primary sub-items: 1.1. Clearly stated research question; 2.1. Population defined; 2.2. Comparison groups defined and justified; 3.1. Exposure - e.g. treatment - is clearly defined; 3.2. Primary outcomes defined; 4.1. Potential confounders are addressed; 4.2. Study groups are compared at baseline; 5.1. Results are clearly presented for all primary and secondary endpoints as well as confounders; 6.1. Results consistent with known information or if not, an explanation is provided; 6.2. The clinical relevance of the results is discussed; 7.1. Potential COI, including study funding, are stated.
Results. The 14 studies identified supported the benefit of AIT in real-life, which persists after treatment discontinuation. However, none of them met all the 7 primary RELEVANT criteria. The main defects were reported in the design (28.6% of studies), measures and analysis (64.3% of studies), and results (78.6% of studies) items, due to selection bias and lack of methods for adjusting controls. Half of the studies did not report on conflict of interest.

**MAIN DEFECTS**

28.6% Study Design  
50% NO Conflict of Interest  
64.3% Measures & Analysis  
78.6% Results
KEY MESSAGES

RELEVANT appears an easy-to-use and sensitive tool for quality appraisal in AIT studies

CALL to ACTION:
there is a need for more robust observational research in AIT

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[Image of diagram and text]

6 | FINAL REMARK

Because of their proven importance and value, we conclude with a

Call to Action to establish more AIT registries with the aim of collecting data in a cohesive way, using standardized protocols. Particular attention should be paid to patient engagement in these trials to obtain high-quality data. This will enable data to be easily shared and

Paoletti G., Di Bona D. et al. Allergy 2021
BSACI Registry for Immunotherapy (BRIT): Providing safe and effective immunotherapy for allergies and urticaria

Sujoy Khan1  
Mamidipudi Thirumala Krishna2,3,4  
Lovelie J. Michaelis5,6,7,8  
Tom C. Dawson9  
Deborah Marliage9  
Anna Thursby-Pelham9  
Leyla Pur Özyiğit10  
Carla Jones10  
Lynne Regent9  
Mich Erlewyn-Lajeunesse11,12

FUNDING INFORMATION
The BSACI has received educational grants from Allergy Therapeutics, ALK-Abelló, and Stallergenes Greer to support the registry.

Khan et al Clin Exp Allergy 2021
FINAL MESSAGE

BIG DATA from AIT REGISTRIES will provide great insights about Molecular Components and AIT Effectiveness

THANKS

PUGGIONI Francesca
RACCA Francesca
LAMACCHIA Donatella
CATALDO Giuseppe
MALIPIERO Giacomo
MARSEGLIA Alessia
LECCHI Antonella
SPINELLO Lina
HEFFLER Enrico
PAOLETTI Giovanni
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