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EMJ Allergy & Immunology

EAACI Congress 2022

Editor's Pick

Biddle et al. discuss the emergence of janus kinase inhibitors for the treatment of rheumatoid arthritis.

Interviews

Establishing New Standards in Hereditary Angioedema: Improving Outcomes Through Routine Prophylaxis, Sorena Kiani

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Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

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Front cover and contents photograph: Prague, Czechia, home of the **EAACI 2022 © Kajano** / stock.adobe.com

Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

It is my pleasure to welcome you to this year's issue of *EMJ Allergy and Immunology*. In this issue, you will read about the latest advances in the field as presented at the European Academy of Allergy and Clinical Immunology (EAACI) Congress, which followed a hybrid format this year and was held in Prague,Czechia, with sessions also available online.

This year's EAACI Congress theme was that of One Health, which examines the links between human health and environmental factors, and transcended across different sessions. New guidelines were presented on environmental science for allergy and asthma which you can read more on, as well as on the impact of climate change and air pollution on human health in a feature article included in this issue. Studies presented included a study on the impact of urbanisation on the prevalence of asthma and allergies, and a study on the impact of a farm environment on the development of allergies in children, both of which are summarised in our congress highlights session.

In our selection of original articles, an opinion article questions the requirement for allergen-specific immunotherapy studies in children, and a review article discusses JAK inhibitors on rheumatoid arthritis. Other articles inlcude a highly engaging review on the role of mast cells in a number of conditions including mastocytosis and urticaria and a couple of interesting case reports including one discussing the frequent use of wipes and multiple allergic sensitisations.

I would like to close by thanking everyone who helped bring this content together: the EMJ in-house team, our authors and peer reviewers, and of course our Editorial Board. Enjoy reading the journal!

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Foreword

Dear Readers,

I would like to present to you the latest issue of *EMJ Allergy & Immunology*. This fantastic compilation of key updates in the field has only been made possible by the hard work of featured authors, peer reviewers, and of course our Editorial Board members.

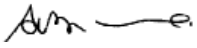
This year's eJournal features compelling updates to the field in the form of research articles, reviews, and features, alongside interviews with experts in the field. Also included is a comprehensive review of the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress 2022, as well as abstract reviews written by the presenters themselves.

The Editor's Pick for this issue is a fascinating article on the topic of JAK inhibitors by Biddle et al. titled 'JAK Inhibitors in Rheumatoid Arthritis'. The authors explore the mechanisms of action of this disease-modifying therapy on rheumatoid arthritis, as well as presenting key evidence on their efficacy. A case of a rare disease known as shiitake dermatitis is explored in a case report by Wu et al. This timely review includes insights into the pathogenesis of this condition, which is expected to increase across the globe with the increased consumption of shiitake mushrooms in Western society.

New research into the central role of mast cells in conditions associated with mediator release is highlighted in an article by Rudenko. This review gives an overview of current knowledge and new information regarding the role of these cells in mastocytosis, hereditary α-tryptasaemia, mast cell activation syndrome, urticaria, and angioedema. A fascinating case report by Bakiri and Mingomataj underlines the links between the frequent use of moist wipes during the COVID-19 pandemic and the development of allergic contact dermatitis.

For those who were unable to attend the EAACI Congress 2022, our independent review gives an overview of the event, featuring key sessions, late-breaking research, and an in-house feature on the topic of climate change and allergy.

As Editor-in-Chief, I would like to thank the authors, peer reviewers, and Editorial Board members who made this journal possible. Their continued support and dedication have made this issue of *EMJ Allergy & Immunology* possible. I hope that you enjoy this collection of key updates, and that they continue to be of value to everyday clinical practice.



Jacques Bouchard

Associate Professor of Clinical Medicine, Université Laval; Allergy Department, La Malbaie Hospital, Quebec City, Canada

EAACI 2022

Review of the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2022

Location: Prague, Czechia
Date: 1st–3rd July 2022
Citation: EMJ Allergy Immunol. 2022;7[1]:8-16. DOI/10.33590/emjallergyimmunol/. https://doi.org/10.33590/emjallergyimmunol/10152128

FOLLOWING the success of the hybrid format at the 2021 European Academy of Allergy and Clinical Immunology (EAACI) congress, it was decided that this year's annual meeting would be held online, as well as in the remarkable city of Prague, Czechia. With 8,000 participants from 120 countries participating in EAACI 2021, Marek Jutel, EAACI President, and Petr Panzner, EAACI Hybrid Congress Chair 2022 both emphasised the benefits of this flexible format, expanding interaction with experts across the globe and improving the outreach of the impressive scientific programme that was on offer at this year's event. EAACI have focused on the development of their Digital Congress Platform, providing a seamless transition between the physical and virtual elements of the meeting.

This year's motto was centred around the One Health approach, which concentrates on establishing the intrinsic links between human health and environmental factors. The innovative approach is the research focus of the EAACI academy, and has gained impetus within the European Commission and World Health Organization (WHO). This has led to new perspectives towards providing solutions to disease transmission and treatment. With the development of various multidisciplinary relationships and initiatives in One Health research, expertise from the perspective of allergy and immunology community was shared throughout EAACI 2022, alongside opportunities for further discussion of this exciting concept.

Over the 3-day event, EAACI had a range of scientific sessions, to attend both in-person and online. Featuring journal highlights from EAACI, hot topic sessions covering late-breaking discoveries in the field, and hybrid interactive workshops which allowed speakers to discuss clinical and translational evidence interactively. Spanning across the discipline, presentations covered fascinating topics including the novel avenues of immunology in the post-COVID era, emerging treatments for relevant conditions including angioedema, and the evolving epidemiology and understanding of food allergies.

"This year's motto was centred around the One Health approach, which concentrates on establishing the intrinsic links between human health and environmental factors."

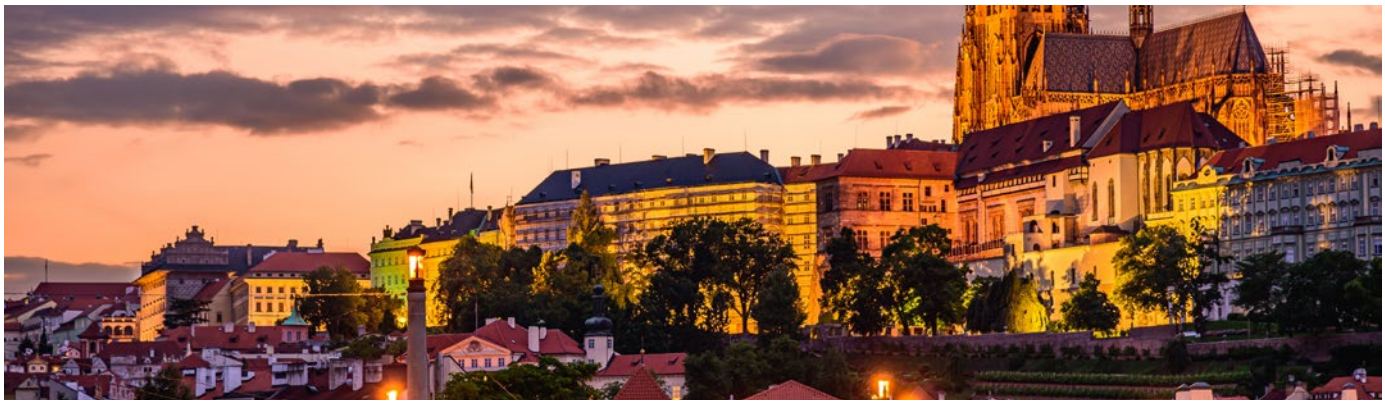
A new addition to this year's congress were the ePosters available on the EAACI Digital Congress Platform. With sustainability and outreach in mind, the publishing of these posters online allowed maximum exposure of fascinating research from over 1,700 delegates. Covering topics including the management of allergic rhinitis, adverse reactions to insect venom, and the impact of gut microbiome maturation on food allergy, these ePosters were an interactive and modern way to share late-breaking findings across the discipline.

An awards ceremony also took place at this year's EAACI congress. The PhARF award was presented to Maria M Escribese, Associate Professor and Vice Dean of Research and Postgraduate Studies, Basic Medical Sciences Department, Universidad San Pablo CEU, Spain. This award recognises young investigators for their outstanding contributions to research, and also offers a research grant, which can fund several projects. The Allergopharma award was also handed out this year. Established in 2000, this award recognises scientific achievement of young scientists in allergy and immunology, and encourage further research. This year, Janice Layhadi, Research Associate, Imperial College London, was given the Allergopharma award for her project entitled 'Precision Immunology and Biomarkers of Allergy and Immunotherapy'. Being the research lead for single-cell multi-omic research, which has resulted in the identification of novel biomarkers, Layhadi's research has prompted several peer-reviewed publications in high-impact journals.

Our independent review of this event gives a comprehensive oversight of the highest quality research on offer at EAACI 2022. The authors of selected standout ePosters have provided key summaries of their research, which are shared in this issue. Covering topics including the management of angioedema, injection-site reactions following the COVID-19 mRNA vaccine, and the prescription of epinephrine auto-injectors, these summaries give fascinating insights into the latest research in the field. An in-house feature on the topic of environmental science in allergy and asthma is also included, giving an overview of current guidelines and sharing perspectives on the One Health approach.

"With sustainability and outreach in mind, the publishing of these posters online allowed maximum exposure of fascinating research from over 1,700 delegates."

Read on for our key insights into the congress, sharing the aforementioned content alongside selected late-breaking news stories. We were delighted to attend this event in-person following the restrictions of the pandemic, and hope to join the allergy and immunology community once again in Hamburg, Germany for EAACI 2023.



How Blue and Green Spaced Can Impact Asthma and Allergic Disease Incidence

DEVELOPING EVIDENCE was presented at the Annual Congress 2022 of the European Academy of Allergy and Clinical Immunology on the impact of growing urbanisation, exposure to air pollution, and the loss of natural environments on disease patterns and prevalence. Non-communicable diseases, such as asthma and allergic diseases were highlighted as particularly impacted by the changing relationship between humans and their surrounding environment.

Previous studies have investigated how the loss of natural spaces and biodiversity can impact dysbiosis of the human microbiota. The holobiont concept underlines the importance of environmental context in the dynamic interaction between humans and their microbiota. The inconsistent evidence produced by previous studies researching the impact of green and blue spaces on development of allergic disease and asthma may be due to variety in geographic location, definition of outcome, and conceptualization of green and blue spaces. However, recent studies have demonstrated that exposure to green spaces at specific points throughout life can be key to protection against allergy and asthma.

In addition, some evidence has suggested that schools and residential neighbourhoods with high exposure to green spaces have a dose-response relationship with lower prevalence of asthma and allergic symptoms. Furthermore, blue spaces have been associated with improvements in human health through lowered environmental hazards and increased physical activity.

“Most of the studies provide evidence that natural spaces and biodiversity may be a protective factor for the development of allergy and asthma, showing that integrating natural elements into cities in a

controlled way and promoting the contact of humans with nature may be an effective strategy to promote human health as well as prevent allergic and respiratory diseases,” explained Inês Paciência, Center for Environmental and Respiratory Health Research, Oulu, Finland.

"In addition, some evidence has suggested that schools and residential neighbourhoods with high exposure to green spaces have a dose-response relationship with lower prevalence of asthma and allergic symptoms."

Though multiple associations have been drawn between environmental influences and allergic disease occurrence no conclusive mechanisms have been articulated. However, several mechanisms have been suggested to potentially explain these effects. These include exposure to air pollution, pollen concentration, the impact of the autonomic nervous system, and immunological responses to the environment. However, further future study is needed to increase understanding of the relationship and the driving mechanisms. ●

Does Sex Affect Disease Severity in Atopic Dermatitis?

"Whilst symptoms were objectively more severe in males, no sex differences in subjective experience and impact on quality of life were identified."

FINDINGS presented at the EAACI Hybrid Congress, Prague, Czechia, 1st–3rd July 2022, by lead author Katharina Zeiser, University of Augsburg, Germany; CK-CARE, Christine Kühne-Center for Allergy Research and Education (CK-CARE), Davos Wolfgang, Switzerland, highlights differences in symptom severity between male and female patients with atopic dermatitis.

Atopic dermatitis is an inflammatory skin condition that has a prevalence of 5-15% in Europe. It causes symptoms such as dry, itchy skin, and sleep disturbance, which have a negative impact on patient quality of life.

Zeiser and colleagues analysed cross-sectional data from 1,011 patients included in the prospective, multicentre, longitudinal, atopic disease study, ProRaD, between 2016 and 2021, in order to determine whether an association between disease severity and sex exists. Of these 1,011 patients, 57% were female, 43% were male, and median age was 39.5 years.

Symptom severity was measured using the affected body surface area, SCORing Atopic Dermatitis (SCORAD), and Eczema Area and Severity Index (EASI) objective symptom measures.

The results showed that objectively, males experienced more severe symptoms than females. These differences were not dependent on age or treatment. No sex differences were found in relation to subjective, patient–reported measurement of symptoms or quality of life. Higher symptom severity was found to be associated with treatment use and lower educational levels in both sexes.

In summary, whilst symptoms were objectively more severe in males, no sex differences in subjective experience and impact on quality of life were identified. The researchers state that further data analysis is required to improve understanding of the biological, psychosocial, and microbiological factors involved in development of atopic dermatitis in both specific patient groups and individuals. This in turn, could lead to development of personalised treatment pathways and help to facilitate improved prevention strategies. Currently, work by the ProRaD team in Bonn on analysis of a sex-specific biomarker is underway in order to achieve a deeper understanding of these findings.

Farm Environments Protect Children from Allergies

RESEARCH HAS found that children who grow up in a farm environment have significant protection from both allergies and asthma. Living on a cattle farm, and consuming raw cow's milk, has been proven to be beneficial.

Presented at the EAACI Annual Congress 2022, in Prague, Czechia, one study reported that a bovine factor specific to different bovine species is involved. Researchers collected dust specimens from several cattle stables. When these samples were evaluated, one predominant protein was discovered, and confirmed as β-lactoglobulin (BLG), the source of which is cattle urine. This major whey protein was also found in dust in the households of the respective cattle farms.

Data suggest that β-lactoglobulin is a bovine-specific acute phase protein, which is associated with the immune regulation aspect of inflammation. In *in vitro* examination, empty BLG was used in healthy donors for the stimulation of peripheral blood mononuclear cells. Researchers found that the proliferation rate was higher, and that a Th2-dominated milieu commenced. When investigators attached zinc to BLG, CD4+ and CD8+ cells were found to be inhibited, which is linked to a Th1-dominated cytokine profile.

In vivo examination went on to prove the anti-allergic properties of BLG-zinc. Investigators treated mice intranasally with stable dust from the initial samples, some of which contained BLG, and some of which did not. In subsequent allergen and sensitisation tests, mice were found to have reduced allergic symptoms.

> **"The type of soil for planting animal feed, the biodiversity of feeding plants and stable environment, the type of feed for the animals and milk processing potentially influence the structure and loading of this protein."**

Isabella Pali-Schöll, Nutritional Scientist at the Department for Comparative Medicine, Messerli Research Institute, Meduni and VetMedUni Vienna, declared: "Our study demonstrates for the first time that an innate immunoregulatory protein, namely β-lactoglobulin, is a novel player in the protective farm effect." She went on: "The type of soil for planting animal feed, the biodiversity of feeding plants and stable environment, the type of feed for the animals and milk processing potentially influence the structure and loading of this protein." ●

Could Platelet Profiles Provide Potential Therapeutic Targets for Personalised Allergy Therapy?

ANALYSIS of platelets from those with severe respiratory allergies has revealed differences in lipid, protein, and mRNA content when compared to platelets from those with milder or no allergy phenotypes.

Lead researcher, Elena Izquierdo, Institute of Applied Molecular Medicine Nemesio Díez, Department of Basic Medical Sciences, Faculty of Medicine, San Pablo CEU University, Madrid, Spain, presented these findings at the EAACI Hybrid Congress, Prague, Czechia, on 3rd July 2022.

Izquierdo and colleagues have previously shown that platelet function is altered in those with severe respiratory allergy phenotypes compared to those with mild/no allergy phenotypes. Since then, they have conducted further research into the differences in platelet content profiles between those with severe and mild/no allergy phenotypes.

Platelet-apheresis and lipid extraction techniques were used to analyse the total lipid and mRNA content of platelets from 26 patients with varying allergy phenotypes in order to assess the role that platelets play in severe allergy. Of the 26 patients enrolled, seven displayed a severe allergy phenotype, nine displayed a mild allergy phenotype, and 10 had a non-allergic phenotype.

Platelets from the seven patients with severe respiratory allergies displayed higher levels of ceramide, phosphatidylinositol, phosphatidylcholine, and sphingomyelin pro–inflammatory lipids, mRNA transcripts, and P–Selectin and IL–17AF proteins when compared to the platelets of those with mild or no respiratory allergy phenotypes.

Given the rising annual incidence of respiratory allergies and the complications associated with them, this research could inspire further research to improve identification and management of severe respiratory allergies.

Izquierdo stated that the results help to "identify novel biomarkers essential for the stratification of patients and to provide novel therapeutic targets for personalised interventions that could prevent the evolution of inflammation to a chronic state."

"The results help to 'identify novel biomarkers essential for the stratification of patients and to provide novel therapeutic targets for personalised interventions that could prevent the evolution of inflammation to a chronic state.'"

The study findings could provide potential targets for novel therapeutics, as well as potentially identify biomarkers indicative of severe allergy. Further research in these areas could lead to reduced disease burden, improved quality of life for patients with severe respiratory allergies, and ultimately, healthcare costs. ●

Validation for Artificial Intelligence in Provocation Tests

ALLERGY is an increasing threat to global health, and affects 20% of Europeans. Y. Yarin and colleagues from the ENT and Allergy Center in Dresden, Germany, and Y. Kalaidzidis, an expert in image analysis, have designed an artificial intelligence (AI)-based method of quantitatively evaluating allergic reactions in conjunctional provocation tests (CPT).

While the threat of allergy is increasing, so is the number of patients who are poly-allergic, resulting in the diagnostics of allergic traits to become more complex. CPTs are widely used due to their clinical evidence, specificity, and sensitivity. However, there is an absence of objective quantitative measurements, which is a huge setback for its use in routine clinical practices. Previous efforts to create a reproducible quantification method for CPTs had never gone beyond research projects and clinical studies due to its complex nature and the amount of labour needed.

However, the progress made in AI, particularly in deep neural networks, provides an opportunity for CPTs to become automatic. AllergoEye, designed by Yarin and colleagues, is an AI-based method that was validated by an open-labelled, prospective, monocentric study of 41 patients, who were exposed to different dilutions of grass allergens. A smartphone camera was used to screen and get images of the patients' eyes. This information was then transferred for quantification and image analysis on a computer. The reactions were then analysed by the medical team, subjectively or qualitatively, and AllergoEye quantitatively measured the results.

"However, the progress made in AI, particularly in deep neural networks, provides an opportunity for CPTs to become automatic."

AllergoEye demonstrated high sensitivity and specificity (98% and 90%, respectively) compared with human estimates; however, tuning the AllergoEye cut-off thresholds significantly increased the specificity (to approximately 97%), highlighting a correlation between patient sensitivity and their sIgE capacity classes, and indicates how they are obvious to see, which was not the case in the subjective and qualitative system scores. Yarin believes that "it could be used for patient selection and controlling the treatment efficiency in clinical studies, as well as for diagnostic and therapy control in routine allergologists' practice." ●

Lack of Understanding Amongst Physicians in the Diagnosis and Treatment of Anaphylaxis

ANAPHYLAXIS is an acute systemic hypersensitivity reaction, with potentially life-threatening outcomes. The variety of clinical symptoms that can be associated with anaphylaxis make it challenging to diagnose, often resulting in a late diagnosis or undetected occurrence. Late diagnosis can have catastrophic consequences; therefore, it is essential that occurrence of anaphylaxis is caught early, and correct treatment options are given. Late-breaking research presented at the European Academy of Allergy and Clinical Immunology (EAACI) 2022 Congress highlighted the insufficient understanding of this reaction by healthcare professionals.

Researchers from the Clinic of Chest Diseases, University of Health Sciences, Derince Training and Research Hospital, Kocaeli, Turkey, carried out a survey with the aim to evaluate 840 physicians' awareness and knowledge of the diagnosis and treatment of anaphylaxis. Of the participants, 42.0% were specialists, 29.9% were general practitioners, and 28.6% were residents. The physicians were asked to identify anaphylaxis symptoms, and results showed that 90% identified skin involvement, 84% respiratory involvement, and 78% identified involvement of the cardiovascular system. Less than 50% of participants associated gastrointestinal and upper respiratory tract involvement with anaphylaxis symptoms.

The main treatment option for anaphylaxis is currently adrenaline. During the questionnaire, 83.3% of participants chose this option, with 69.6% recognising the correct route of administration, and 76.4% the application site for adrenaline. Sixty-one per cent of physicians accurately identified the dose of adrenaline therapy, and 48.7% stated that there was no absolute contraindication for the use of adrenaline. Resident physicians had the highest rate of accurate answers regarding dosage and administration, perhaps reflecting the specific education provided during residency. Cihan Örçen, contributing study author, noted: "Anaphylaxis should be considered as a whole with correct diagnosis and correct treatment."

"Sixty-one per cent of physicians accurately identified the dose of adrenaline therapy, and 48.7% stated that there was no absolute contraindication for the use of adrenaline."

Study observations highlighted the areas in which knowledge was lacking. The low identification of the upper respiratory and gastrointestinal tracts as symptoms for diagnosis could reflect the inadequate use of adrenaline. The results also emphasised the need for continued education to improve the widespread knowledge of healthcare professionals in the diagnosis and treatment of anaphylaxis. ●

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Environmental Science in Allergy and Asthma

Authors:	Theo Wolf, Senior Editorial Assistant
Citation:	EMJ Allergy Immunol. 2022;7[1]:18-20. DOI/10.33590/emjallergyimmunol/10091307. https://doi.org/10.33590/emjallergyimmunol/10091307.

Environmental science in allergy and asthma was a topic discussed at this year's European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress 2022, taking place between 1st–3rd July. Of particular clinical relevance was the presentation on climate change, air quality, and health, as well as the presentation on the recent EAACI guidelines addressing the impact of the environment on allergic diseases and asthma from inception to severity.

IMPACT OF CLIMATE CHANGE AND AIR POLLUTION ON HUMAN HEALTH

Stephen Holgate, Medical Research Council (MRC) Clinical Professor of Immunopharmacology, University of Southampton, UK, discussed the importance of climate change on the rising incidence of allergy and allergic diseases, and also the direct effect of air pollution on asthma and other noncommunicable diseases.

Regarding allergy, Holgate began by summarising the findings of a 2021 study that analysed annual pollen integrals and the pollen season start date across 60 sites in North America between 1990 and 2018. During this timeframe, an increase in the total amount of pollen released, as well as earlier start dates, were observed across the majority of the continent. He emphasised that this becomes even more apparent when climate change models are fitted to the data in predictive modelling. Specifically, increases in atmospheric CO_2 are expected to have a dramatic effect on pollen production. "It is the CO_2 going up that's making a difference, but CO_2 isn't of course the only climate change emission we are concerned about," said Holgate. Overall, projections indicate that ragweed pollen allergy will become a common health problem across much of Europe. In addition, sensitisation to ragweed is expected to more than double from 33 million to 77 million people by 2041–2060.

Holgate then spoke about a 2017 study that explored the relationship between air pollution and mortality among beneficiaries of Medicare, the government national health insurance programme in the USA. In the entire Medicare population, there was significant evidence of adverse effects related to exposure to fine particulate matter less than 2.5 µm in diameter ($PM_{2.5}$) and ozone at concentrations below current national standards. "There are no safe levels of any of these pollutants on human health," explained Holgate. Interestingly, the effect was most pronounced in people from racial minorities and those with low income. Based on these and similar findings, the World Health Organization (WHO) in 2021 implemented new air quality guidance limit values for $PM_{2.5}$ and nitrogen dioxide (NO_2). "They've come

to dramatic reductions, halving the $PM_{2.5}$ limit value and dividing by four the NO_2 value," said Holgate. In the UK, even achieving the previous 2005 air quality limits for $PM_{2.5}$ would have substantial benefits for human mortality and morbidity. Further, achieving an annual average $PM_{2.5}$ concentration of 10 µg/m³ (WHO-10) across the UK by 2030 would result in approximately 20 fewer infant deaths per year, 3,100 fewer new cases of coronary heart disease per year, and 8–9 weeks longer life expectancy.

Holgate summarised by underlining the importance of health professionals in promulgating and encouraging societies to clean up the air, improve climate statistics, and enhance environmental conditions and quality of life.

EAACI GUIDELINES ON ENVIRONMENTAL SCIENCE FOR ALLERGY AND ASTHMA

Ioana Agache, Transylvania University of Brașov, Romania, started by listing the five working groups involved in the development of the guidelines and explaining the role of each. An atmospheric science working group explored the cost of illness for pollen-induced asthma; whether information on pollen could improve and forecast allergic rhinitis and allergic asthma outcomes; the relationship between extreme temperature events and asthma exacerbations; and the effect of heavy traffic and smoking on asthma. An ecology working group looked at whether exposure to microplastics and pesticides impacts asthma; whether exposure to dishwasher detergents increases the risk of food allergies and eosinophilic oesophagitis; whether greenness in urban environments can prevent the development of allergic diseases and asthma; and whether living on traditional farms, parasite infestation, and viral infection impact the development of allergic diseases and asthma. A human–environment interaction and social science working group investigated whether regiotypes exist in nasal polyposis, pollen allergy, and atopic dermatitis; whether migration, lifestyle and residence, and modern living impact the development and incidence of allergic diseases; and the effects of breastfeeding, food additives, and emulsifiers on the incidence of allergic diseases. A regulatory group addressed the

economic and political dimensions of the recommendations and the possibility of an integrated surveillance network. The fifth working group focused on deployment of artificial intelligence and machine learning to develop a c ausality model.

Concentrating on pollen exposure and asthma-related outcomes, Agache highlighted that severe asthma exacerbations were divided into lag 0, lag 1 to 3, and lag over 3. The certainty of evidence was highest (moderate level of evidence) for severe asthma exacerbations within the first 1–3 days of exposure. Because of the moderate-quality evidence, reducing or avoiding exposure to pollen should be recommended to reduce the risk of severe asthma exacerbations. Specifically, FFP2 masks may be used to reduce the risk of pollen-induced asthma exacerbations. From a public health perspective, emergency departments and other asthma-related services should be strengthened during the grass, ragweed, and birch pollen seasons, and also in thunderstorm asthma. Finally, Agache noted that dispersion models might be recommended for a better prediction of exposure risk.

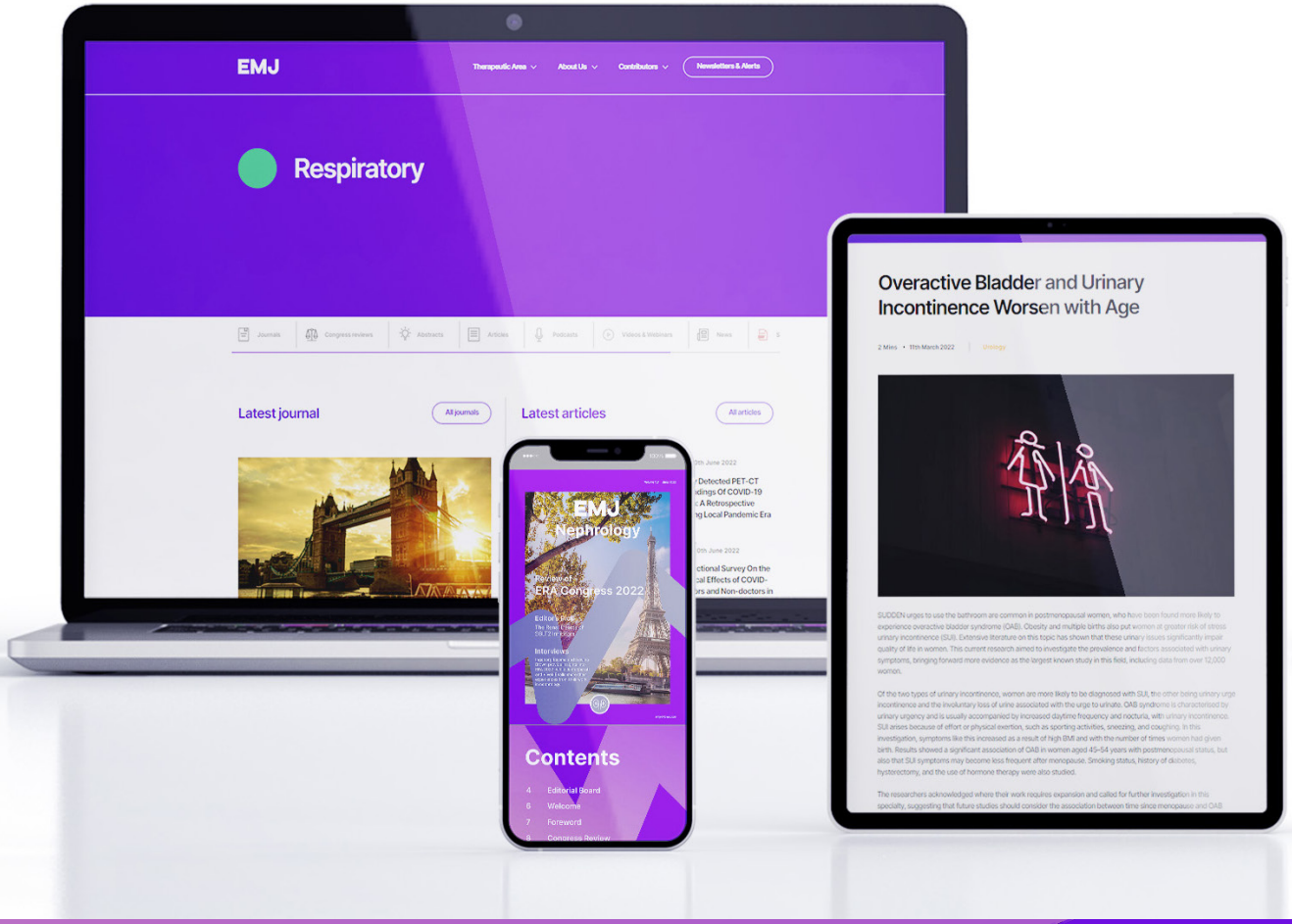
Interestingly, the level of evidence for other asthma-related outcomes was either very low or low. "We have better recommendations for severe exacerbations than we do for moderate exacerbations, asthma control, and lung function," noted Agache.

Agache concluded her presentation by considering how to intervene. Pollutant information should be incorporated in pollen information systems, pollen concentration might be recommended as a reliable proxy of pollen exposure, a real-time pollen count might be recommended for managing pollen-induced asthma, and pollen monitoring networks may be recommended for providing exposure data at the population level. Agache also stated that accurate and consistent pollen counting should be recommended.

"Of particular clinical relevance was the presentation on climate change, air quality, and health as well as the presentation on the recent EAACI guidelines addressing the impact of the environment on allergic diseases and asthma from inception to severity."

CONCLUSION

The environment can support health through key pillars of resilience, namely the diet, microbiome, and epithelial barrier. Enhancing environmental health through the incorporation of clean air as a priority within climate action could help combat allergic diseases and asthma, which are environment-driven entities with life-long impacts. Going forward, the development of high-quality, evidence-based guidelines and the implementation of One Health and Planetary Health policies should be prioritised.



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Reconsider the Art of Allergen Immunotherapy

This symposium took place on 2nd July 2022, as part of the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress held in Prague, Czechia

Chairperson: Susanne Lau[1]

Speakers: Stephanie Dramburg,[1] Marek Jutel,[2,3] Petra Zieglmayer[4]

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Meeting Summary

This symposium took place during the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress, held in Prague, Czechia, in July 2022. Stephanie Dramburg, Medical Doctor at Charité Universitätsmedizin, Berlin, Germany, explained that the traditional diagnostic work-up for allergic rhinoconjunctivitis (AR) comprises retrospective clinical history and allergen exposure assessment, extract-based diagnostics, component-resolved diagnostics (CRD), which enables markers of genuine sensitisation to be distinguished from markers of cross-reactivity, and confirmation of clinical relevance. She highlighted that molecular IgE assessment supports the diagnostic work-up and personalised risk assessment in complex cases and that confirmation of clinical relevance of IgE results is key. Furthermore, broadening of a serum IgE response is indicative of 'molecular spreading'. Dramburg considered that digital technologies have the potential to enhance medical decisions at the point-of-care via targeted patient information, guideline- and evidence-based clinical knowledge, and prospectively collected patient- and sensor-generated data. Marek Jutel, Medical Professor at Wroclaw Medical University, Poland, and the ALL-MED Medical Research Institute, Wroclaw, Poland, described that patients with allergies show different clinical pictures due to differing sensitisation profiles assessed at the molecular level. He noted that patients with allergies react differently to different allergen doses and allergen immunotherapy (AIT) preparations, and minor/intermediate allergens are necessary, in addition to major allergens, for optimal clinical efficacy. Jutel described that allergens that are decisive for AIT efficacy are defined in grass pollen but are not yet determined for other allergen sources such as birch and house dust mite (HDM). Petra Zieglmayer, Medical Professor at Karl Landsteiner University, Krems, Austria, and Head of Vienna Challenge Chamber, Austria, discussed that patients with allergies show complex molecular sensitisation profiles and that extract preparations from different manufacturers vary in terms of allergen composition, with major and intermediate allergens not always detectable. She clarified that optimal efficacy of AIT may only be expected from preparations containing all relevant allergen components in sufficient amounts. Zieglmayer proposed that the target should be to find a match between the patient molecular sensitisation profile and the allergen preparation and that this can be achieved.

Patients' Phenotype Assessment: A Chance for Digital Technologies?

Stephanie Dramburg

Dramburg explained that the traditional diagnostic work-up for AR comprises retrospective clinical history and allergen exposure assessment, extract-based diagnostics, CRD, and confirmation of clinical relevance. Focusing on retrospective clinical history, Dramburg pointed out that patients already use digital technology in the form of calendars on their phones to help them remember and record their symptoms (date, location, and pollination season).

In regard to retrospective exposure assessment, Dramburg described that symptom seasonality is associated with allergen exposure and there is little overlap between the different pollen seasons in Germany so far.[1] Therefore, the agents eliciting symptoms can generally be identified according to when symptoms occur. However, Dramburg highlighted that pollination periods are expanding and that countries in northern and central Europe need to be prepared to see patterns already found in southern Europe (e.g., Italy), with overlapping pollen seasons that complicate the identification of the allergens eliciting symptoms.[2]

This overlapping pollination pattern is also reflected in the patient sensitisation profiles in southern Europe. In a study by the Italian Paediatric Allergy Network (I-PAN), in which 1,360 children aged 4–18 years were recruited, over 80% of participants had a positive skin prick test (SPT) result to ≥3 pollens and almost 50% reacted to ≥6 pollens.[3] Dramburg noted that it would be difficult to prescribe immunotherapy in such cases, as ascertaining the correct allergen to target would be challenging, and this is where CRD is important: the use of recombinant or highly purified native allergenic molecules enables markers of genuine sensitisation to be distinguished from markers of cross-reactivity.

Population data from the German Multicentre Allergy Study birth cohort[4] of 820 children (of 1,314 recruited) indicated that the prevalence of IgE sensitisation to grass pollen starts to rise before the onset of clinical symptoms, mainly for major allergens such as *Phleum pratense* (Phl p) 1 and 5, but also over time for minor and cross-reactive molecules, including Phl p 11 and 12. Dramburg questioned what this population data means for individual patients and discussed the case of a paediatric patient as a clinical example.[5] The first blood sample from this patient was taken at age 3 years, when the patient had no allergy symptoms but already had specific IgE (sIgE) to Phl p 1. Onset of symptoms was at age 6 years, when there was evidence of a broadening of sIgE response to Phl p 1, 2, and 4; so-called 'molecular spreading'. At age 10 years the patient was broadly sensitised, including to cross-reactive molecules, and was considered to potentially react to other botanic sources.

Further population data from the German Multicentre Allergy Study birth cohort[4] showed that the molecular spreading phenomenon was also evident for HDM allergenic molecules, with Der p 1, 2, and 23 considered to be 'initiator molecules' as they appear early in the sensitisation process.[6]

The transition of a patient along their sensitisation journey is one-way, towards a broader sensitisation spectrum, with no patients reverting to a narrower immune response.[6] Dramburg disclosed that molecular IgE diagnostics help give clinicians a better idea of where the patient is in their sensitisation journey, i.e., are they still mono-sensitised, do they recognise several allergens or allergenic proteins (oligo-/poly-sensitisation), is there any response to marker molecules (e.g., *Dermatophagoides pteronyssinus* [Der p] 23 as an indicator of asthma risk), or are there markers of cross-reactivity?

The use of CRD has a significant impact on the selection of the AIT formula. In an I-PAN study of 651 children with moderate-to-severe AR, clinicians initially based diagnosis and therapeutic decisions on SPT results; however, when CRD data were available, the decision about the AIT formula was changed in up to 18% of cases.[7]

Dramburg then discussed confirmation of the clinical relevance of molecular test results, which for AR involves nasal[8] or conjunctival[9] allergen provocation tests. These tests can be challenging and time-consuming in patients who are poly-sensitised. In such cases, symptom recording by patients using digital technology, such as an app that combines a symptom diary (electronic [e]-diary) with pollen and weather data, may help clinicians to better understand the phenotype of their patients.

Two patients who were sensitised to multiple seasonal allergens (as shown by SPT results) with overlapping pollination periods were discussed. In these cases, the use of molecular diagnostics did not help to narrow down the likely allergens eliciting the symptoms.[10] Therefore, the patients were asked to monitor their symptoms themselves and pollen exposure was monitored separately. The rhinoconjunctivitis total symptom score for the two patients correlated perfectly with exposure to a specific allergen (olive pollen for one patient and grass pollen for the other).[10] According to Dramburg, the data from patient-recorded symptom e-diaries are helpful for clinicians when deciding which AIT to use first, or for defining which is the clinically relevant agent for the patient.

Dramburg proposed a clinical decision support system (CDSS) could be used to assist clinicians in their day-to-day practice.[11] A digital system algorithm takes into account factors such as clinical history and allergen exposure assessment, extract-based diagnostics, CRD, and evidence-based guidelines, as well as

treatment settings and local adaption of the support system according to the clinician's personal experience.[11] The patient is repeatedly re-evaluated according to the algorithm to monitor success and ensure the timeliness of any treatment adaptions.

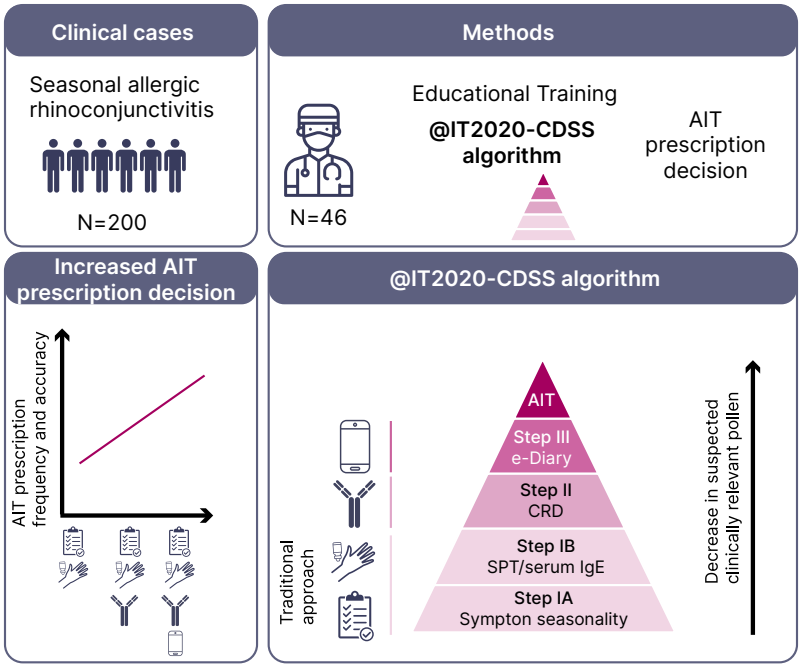
There have been different approaches for CDSS algorithms in allergic rhinitis, including an expert opinion-based decision algorithm for symptomatic treatment (MASK e-CDSS) from the Allergic Rhinitis and its Impact on Asthma (ARIA) consortium,[12] and a diagnostic algorithm based on CRD and e-diaries (@IT2020-CDSS) that was evaluated in a pilot study in Italy by Arasi et al.[13]

As part of the @IT.2020 multicentre study,[14,15] 815 patients aged 10–60 years with seasonal allergic rhinitis were recruited in seven countries in southern Europe. Patients completed clinical questionnaires and underwent SPTs and sIgE testing. A symptom diary app (AllergyMonitor, Technology & Project Software [TPS] Production, Rome, Italy) was installed on their phones.[14] Patients were specifically asked to monitor their symptoms according to their suspected relevant allergen season (based on SPT results and clinical history) rather than throughout the year, and the resulting information was communicated to the patients and provided to clinicians to see if it improved decision-making.[14]

Dramburg emphasised that the focus of digital technology should ideally support the patient–clinician relationship as part of a blended care approach, where technology assists but does not replace the clinician. In the @IT.2020 multicentre study,[14,15] for example, clinicians prescribed symptom monitoring as diagnostically necessary. Patient adherence to symptom e-diary recording in this blended care setting was very high, with around 80% adherence during a period of over 70 days.[16]

Dramburg summarised the three steps in the CDSS as clinical history (symptom seasonality) and SPT and/or sIgE; CRD; and e-diary pollen exposure, with the aim to provide more precise prescription of AIT based on good data. In the pilot study,[13] a workshop with allergy specialists and general practitioners showed that knowledge gleaned from each of the three steps of the CDSS was associated with improved

Figure 1: Three steps in the Clinical Decision Support System.[13]



AIT: allergen immunotherapy; CRD: component-resolved diagnostics; e-Diary: electronic diary; SPT: skin prick test.

diagnostic performance. This indicated the theoretical potential of the CDSS for supporting clinicians in their diagnostic decision-making (Figure 1).

The clinicians' opinions of the usability of the CDSS were then explored. The allergy specialists and general practitioners considered that the accuracy of AIT prescription can be improved with a CDSS, the proposed algorithm makes sense, and it enhances traditional diagnostics. Notably, they also questioned the reliability of clinical history that is retrospectively assessed.

Dramburg concluded that molecular IgE assessment supports the diagnostic work-up and personalised risk assessment in complex cases and that confirmation of clinical relevance of IgE results is key. Software tools and mobile solutions have the potential to enhance medical decisions at the point-of-care via targeted patient information, guideline- and evidence-based clinical knowledge, and prospectively collected patient- and sensor-generated data. Dramburg emphasised that patients or their caregivers are not recommended to record symptoms until they have clearly occurred to prevent patients being considered as "sicker than they are."

Matching Molecular Profiles and Clinical Outcomes

Marek Jutel

Jutel reported that patients show different sensitisation profiles, which can be origin-dependent. This is illustrated in a study by Muddaluru et al.[17] conducted in Canada, Europe, South Africa, and the USA, which showed different IgE responses to HDM allergens based on geographical location. Differences in molecular profile are also seen in patients according to clinical diagnosis. Resch et al.[18] showed that the IgE profiles to individual HDM allergens of children with or without asthma with HDM allergy differed in terms of IgE binding prevalence and the number of allergens recognised. Interestingly, the patients with asthma were predominantly sensitised to a larger number of allergens in the allergen source than the patients without asthma.[18]

Jutel noted that there are several biomarkers of humoral and cellular immune response that can be assessed during the course of AIT, including sIgE, sIgG4, interleukin-4 (IL-4)+ cells, regulatory T cell response, and eosinophil count.[19] Jutel referred to a study by Shamji et al.[20] that showed the time course and dose-dependency of clinical outcome, allergen-specific IgG4 antibody levels (measured by enzyme-linked immunosorbent assay) and serum inhibitory activity (measured using the IgE-facilitated allergen binding assay [IgE-FAB], which assesses functional IgG4) during subcutaneous grass pollen AIT. Levels of functional IgG4 correlated closely with clinical response to AIT.[20]

Jutel explained that different allergen extracts induce dissimilar grass pollen allergen-specific IgG responses in an experimental model in rabbits,[21] because of the variations in the composition and number of allergens in these preparations. Following on from this preclinical observation, Jutel posed the question: Why do patients with different molecular profiles respond differently to different AIT preparations? In addressing this question, he highlighted the disparity between traditional allergen extracts and molecular extracts. Traditional extracts involve extraction and purification (e.g., of a grass sample) and then the composition and strength (amount of allergen) of the extract is evaluated. In contrast, the exact qualitative and quantitative composition of molecular extracts (recombinant preparations) is established a priori by the manufacturer and is known to the clinician and the regulatory agency.[22]

In consideration of a further question about how patients with different molecular profiles react to a molecular extract, Jutel reiterated that there are major grass pollen allergens such as Phl p 1 and 5, to which the majority of patients are sensitised; intermediate allergens, including Phl p 2, 4, and 6, to which some patients are sensitised; and minor allergens, like Phl p 3, 7, 11, 12, and 13, to which few patients are sensitised.

The link between patients' molecular profiles, a molecular extract and clinical outcomes was assessed post-hoc in a double-blinded, placebo-controlled study (AL0704rP; EudraCT 2007-003208-37; [Allergopharma GmbH & Co. KG, unpublished data]), which involved a recombinant equimolar preparation of Phl p 1, 2, 5a, 5b, and 6. The clinical outcome after AIT was assessed in the context of the sensitisation profiles of the

patients before the initiation of AIT treatment. The primary endpoint was rhinoconjunctivitis symptom medication score (RC-SMS). Jutel pointed out that, importantly, there was no Phl p 4 allergen in this preparation.

According to Jutel, numerous questions arose while analysing the data from study AL0704rP (Allergopharma GmbH & Co. KG, unpublished data), including whether the composition of the allergen cocktail was optimal (or were any relevant allergens missing), whether only major allergens are necessary for optimal efficacy, or does such a strong cocktail of allergens induce new sensitisations in patients, and whether there are any differences in efficacy in patients with broad (poly-) versus mono-/oligo-sensitisation (Nandy, unpublished data).

Jutel explored whether the sensitisation profile of the patient before AIT could be regarded as a prognostic biomarker for treatment efficacy. Analysis of the molecular profile of participants who had ≥70% improvement in RC-SMS after 2 years of active treatment (120 µg allergen, which is six-times higher than the 20 µg considered sufficient to induce a response) showed that sensitisation to Phl p 1 and 5 is important, with sensitisation to at least one of these allergens necessary for AIT efficacy (Allergopharma GmbH & Co. KG, unpublished data). There was a low level of sensitisation to minor and intermediate allergens (Phl p 7, 11, 12, and 13 [Allergopharma GmbH &Co. KG, unpublished data]); however, Jutel clarified that these allergens are still important and cannot be disregarded, i.e., it is not only major allergens that are necessary for optimal efficacy. Supportive data on the importance of Phl p 1 and 5 as predictive biomarkers for treatment efficacy were provided by a study of sublingual immunotherapy, where patients with low pre-treatment sIgE to Phl p 1 or 5 presented no clinical benefit in the first pollen treatment season.[23]

Those participants who had ≥40% deterioration in RC-SMS after 2 years of active treatment were sensitised at inclusion to Phl p 4, which was not included in the study preparation (Allergopharma GmbH & Co. KG, unpublished data). Jutel stated that the composition of the allergen cocktail was not optimal and Phl p 4 is essential in an AIT preparation for assessment of theprojected treatment efficacy.

Two-thirds of patients (10 out of 15) who were not sensitised to Phl p 4 at inclusion showed improvement in RC-SMS after 2 years of active treatment (Allergopharma GmbH & Co. KG, unpublished data). The remaining five patients who showed deterioration in RC-SMS were sensitised to Phl p 1 but not to Phl p 5 (Allergopharma GmbH & Co. KG, unpublished data), which indicates that sensitisation to Phl p 5 before AIT may be of higher importance than that to Phl p 1 for treatment efficacy.

Jutel then considered whether the recombinant allergen cocktail induces new sensitisations because of a mismatch between the composition of the preparation and the patient's sensitisation profile before treatment.[24] A study of the sensitisation pattern of 176 children showed that there was a 100% match to cocktail composition in only 4% of patients, and 67% of patients were sensitised to either more allergens than were in the cocktail, or some or no allergens that were in this preparation.[25] Although this may cause concern in terms of raising new sensitisations when using AIT preparations containing more allergens than the patient is sensitised to, the study confirmed that this is not the case by showing that there were no significant differences in new sensitisations between active- and placebo-treated patients (Table 1 [Allergopharma GmbH & Co. KG, unpublished data]). Jutel also clarified that no differences in response to allergen preparations have been seen in patients who have poly- versus mono-/oligo-sensitisation (Nandy, unpublished data).

Jutel concluded that patients with allergy show different clinical pictures probably due to their different sensitisation profiles assessed at the molecular level. Patients with allergy react differently to different allergen doses and AIT preparations, and minor/intermediate allergens are necessary, in addition to major allergens, for optimal clinical efficacy. There are several unmet needs in AIT. Allergens that are decisive for AIT efficacy are defined in grass pollen to be Phl p 1, 4, and 5; however, those for other allergen sources (birch and HDM) are yet to be determined. Jutel assumed that it may be possible to design a universal allergen-based preparation for grass and birch pollen or cat allergy, but not for sensitisation to complex allergen sources (e.g., mites, moulds).

Table 1: New sensitisations in patients not sensitised against the respective allergen before treatment.

Allergen	Group	N patients sensitised after AIT/N patients not sensitised before AIT	%
Phl p 1	Placebo	0/1	0.0
	80 µg	1/2	50.0
	120 µg	0/0	0.0
Phl p 2	Placebo	3/14	21.4
	80 µg	3/11	27.3
	120 µg	2/14	14.3
Phl p 5a	Placebo	1/2	50.0
	80 µg	0/4	0.0
	120 µg	2/6	33.3
Phl p 5b	Placebo	0/3	0.0
	80 µg	0/5	0.0
	120 µg	2/6	33.3
Phl p 6	Placebo	2/20	10.0
	80 µg	2/17	11.8
	120 µg	4/20	20.0

Allergopharma GmbH & Co. KG, unpublished data.

AIT: allergen immunotherapy; Phl p*: Phleum pratense.*

Optimal Allergen Compositions: A Benefit for the Patient?

Petra Zieglmayer

Zieglmayer emphasised that commercial allergen extract preparations used for diagnostics and treatment are derived from natural materials and their molecular composition varies regarding allergen content and concentration.[26] Also, as explained by Jutel using grasses as an example, it is important to consider minor and intermediate allergens as well as major allergens for these extracts. The importance of Group 5 allergens for the success of AIT is recognised;[27] however, that of Group 1 allergens is still unclear, and these allergens are underrepresented in some commercial extracts because of problems with extractability, degradation in stored extracts, and diverse immunogenicity.[27] According to Zieglmayer, the allergenicity of Group 5 allergens in terms of induction of a protective IgG4 response is far higher than it is for Group 1 allergens, depending on the allergen content and formulation of the preparation. Therefore, there is a need to optimise the content of preparations and their adaptability.

Zieglmayer noted that commercially available HDM extracts are also heterogenous, with the composition of these extracts depending on the source of material used (e.g., whole mite cultures, including faeces, versus a purified mite body source material with no faeces).[28] She indicated that extracts that differ in terms of major and intermediate mite allergen content may produce different benefits for patients when used as AIT and questioned how this can be managed.

Focusing on the production process, Zieglmayer described how the timing and method of extraction impacts on allergen content.

For example, extracts from different harvests of birch pollen material have been shown to have naturally diverse composition, and process steps like the extraction time impact on the allergen content.[29] Therefore, there is a clear batch-to-batch variability between extracts derived from natural materials that Zieglmayer suggested needs to be managed accordingly, through adapting production processes to optimise the composition of the preparations. Another quality assurance measure is to fully characterise the composition of allergen preparations using mass spectrometry.[30] This provides further information about the match between sensitisation profile of the patient and composition of the preparation required for treatment.

Zieglmayer presented the allergen components in different grass pollen preparations (Table 2) and emphasised that it is possible to have all relevant grass allergens in these preparations, whether they are native or allergoid, or subcutaneous or sublingual, but this is not a given.[31] As shown by the crosses in Table 2, some important allergens may be missing, which may impact on the efficacy of immunotherapy.[31]

Analysis of the complete allergen spectrum of HDM preparations showed that it is possible to include all relevant HDM allergens whether it is a natural, unmodified, or a modified (allergoid) preparation,[32-34] which indicates that the composition is not dependent on the formulation. However, Zieglmayer stressed that clinicians should be aware that HDM preparations from different manufacturers vary (Table 2), and some may lack relevant allergens to which patients are sensitised.[31]

Table 2: Allergen components in different grass pollen preparations and different house dust mite preparations.[31]

Grass pollen preparations									
	Allergopharma allergoid (grasses)		SCIT allergoid 2 (grasses)		SCIT allergoid 3 (grasses)		SCIT native (grasses and rye)		SLIT (grass)
Group 1	✓		✓		✓		✓		✓
Group 5	✓		×		✓		✓		✓
Group 2	✓		✓		✓		✓		✓
Group 4	✓		✓		×		✓		✓
Group 6	✓		✓		✓		✓		✓
Group 3	✓		✓		✓		✓		✓
Group 7	✓		✓		✓		✓		×
Group 11	✓		✓		✓		✓		✓
Group 12	✓		×		✓		✓		✓
Group 13	✓		✓		✓		✓		✓
House dust mite preparations									
	Allergopharma allergoid (D.p.)	Allergopharma allergoid (D.p.+D.f.)	Allergopharma native extract (D.p.)	Allergopharma native extract (D.p.+D.f.)	SCIT allergoid 2 (D.p.+D.f)	SCIT allergoid 3 (D.p.)	SCIT native extract (D.p.)	SCIT native extract (D.p.+D.f.)	SLIT (D.p.+D.f.)
Group 1	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 2	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 23	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 4	✓	✓	✓	✓	✓	×	✓	✓	✓
Group 5	✓	✓	✓	✓	✓	×	×	×	×
Group 7	✓	✓	✓	✓	✓	×	×	×	✓
Group 21	✓	✓	✓	✓	✓	×	×	×	×
Minor allergens	26 of 29	27 of 29	26 of 29	27 of 29	22 of 29	11 of 29	7 of 29	11 of 29	14 of 29

Dark blue: major allergen; light blue: intermediate allergen; white: minor allergen.

D.f.: *Dermatophagoides farinae*; D.p.: *Dermatophagoides pteronyssinus*; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy.

As part of a discussion on the impact of treatment composition on the efficacy of AIT, Zieglmayer pointed out that there are grass pollen species that are more relevant for northern than southern Europe and vice versa,[35] and she questioned whether these species are interchangeable or whether it is sufficient to use one representative species for all patients, irrespective of their location. She remarked that there is a close phylogenetic relationship between the sweet grass species in northern Europe.[36] However, a grass species from southern Europe (*Cynodon dactylon* or Bermuda grass) shows low cross-reactivity with the northern European sweet grasses because it does not contain Group 5 allergens and has different Group 1 epitopes.[37]

Zieglmayer highlighted that the immune system can differentiate between grass pollen species, and that Timothy grass (Phl p; a species that is always included in testing) is not representative of all grass species in terms of allergen composition.[38] How this impacts on management of patients regarding AIT was investigated in a small study in which patients from northern and southern Europe received one- or five-grass pollen sublingual immunotherapy tablets.[39] Inhibition of IgE binding to pollen allergens from 12 grasses was significantly stronger with the five-grass than with the one-grass pollen tablet ($p<0.0001$), with five out of six patients managing inhibition, regardless of whether patients were considered as a whole or by geographical area.[39] The one-grass pollen tablet may be sufficient for most patients to manage the inhibition of a standard 12-grass pollen mix but the remaining patients (one out of six) may not be covered adequately having received just one representative grass pollen rather than a mixture of grass pollen species.

Referring again to mites, Zieglmayer stated that molecular HDM sensitisation profiles are complex,[40] so there is likely no one-size-fits-all solution. Patients who were treated subcutaneously with a standard mite preparation for 1 year in a placebo-controlled, prospective study were evaluated post-hoc for their sensitisation profiles against 12 Der p allergen components at inclusion (three major allergens [Der p 1, 2, and 23], four intermediate allergens [Der p 4, 5, 7, and 21], and five minor allergens [Der p 10, 11, 14, 15, and 18]).[41] According to Zieglmayer, the results were surprising because patients developed an immune response (HDM-specific IgG) against Group 1 and 2 major allergens, whereas the level of IgG response was not different from that in the placebo group for Group 23 or the intermediate allergens, Der p 5, 7, and 21 or minor allergens.[41] Therefore, only the former two major allergens were considered to be present in sufficient amounts in the preparation. This was clinically relevant as only patients who were oligo-sensitised to Group 1 and 2 HDM allergens showed clinical benefit after 1 year of treatment.[41] In contrast, standard patients with a complex profile showed no such clinical benefit after 1 year of treatment. Clinical benefit of subcutaneous immunotherapy, therefore, depends on a fit between the patient's molecular sensitisation profile and the extract molecular profile. One option to achieve this fit, therefore, is to treat patients with modern preparations that contain all relevant allergens.

Notably, a modern HDM tablet preparation with a fractioned composition has shown significant and persisting clinical improvement, with the marketed dose associated with a significant reduction in nasal, ocular, and asthma symptoms within only 8 weeks of treatment, and the improvement maintained at 1-year of follow-up.[42,43] These results indicate a match between the sensitisation profile of the patient and the allergen composition of the preparation.

Zieglmayer stated that there is a general need to evaluate the relevance of formulations *per se* and how dose-dependent effects are but 'the composition counts'.

Zieglmayer concluded that patients with allergy show complex molecular sensitisation profiles and that extract preparations from different manufacturers vary in terms of allergen composition, with major and intermediate allergens not always detectable even by mass spectrometry. Optimal efficacy of AIT may only be expected from preparations containing all relevant allergen components in sufficient amounts. The target should be to find a match between the patient molecular sensitisation profile and the allergen preparation, and this can be achieved.

Concluding Remarks from the Chair

Susanne Lau

Susanne Lau, Professor at Charité Universitätsmedizin, Berlin, Germany, summarised that patients show different patterns of sensitisation, particularly for grass pollen and HDM allergens, and several allergens play a role. She also referred to the important differences in allergen extract preparations. Lau suggested that these considerations and the data presented may create confusion for prescribers of AIT in terms of whether CRD should be performed for all patients with grass pollen allergy, and that, for now, it is best to choose an extract that includes all relevant allergens. Other considerations she raised included how could digital technology help clinicians to be more precise about the significance of sensitisations, how strongly should clinicians encourage patients to record data, how much data should they record, and in which way will clinicians use the patient-recorded data. Questions such as these will direct future research in this evolving area to enable optimal patient care.

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Changing the Way Babies Eat: Supporting Early Allergen Feeding Around the World

This symposium took place on 1st July 2022, as part of the European Academy of Allergy and Clinical Immunology (EAACI) Congress in Prague, Czechia

Chairpeople:	Angela Claver Monzón[1]
Speakers:	Andrea Mikkelsen,[2] Kari Nadeau,[3,] Wendy Sue Swanson[3,4]

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2. University of Gothenburg, Sweden
3. The Sean N. Parker Center for Allergy and Asthma Research, Stanford University School of Medicine, California, USA
4. Before Brands, Inc., Menlo Park, California, USA

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Meeting Summary

This symposium occurred during the European Academy of Allergy and Clinical Immunology (EAACI) Congress, 2022. Angela Claver Monzón from the Hospital Universitari Quiron Dexeus, Barcelona, Spain, welcomed attendees and gave a brief introduction to the topic of food allergy prevention in children. Andrea Mikkelsen from the University of Gothenburg, Sweden, highlighted the importance

of diet diversity and the early introduction of food allergens to infants before discussing some of the challenges associated with this. Kari Nadeau from The Sean N. Parker Center for Allergy and Asthma Research, Stanford University School of Medicine, California, USA, described the results from a study that evaluated different strategies for the early introduction of food allergens. She highlighted that consumption of even small quantities of a multi-allergen mixture for 1 year was associated with improvements in subsequent food challenge reactivity compared with single or double food introductions. Wendy Sue Swanson, also from The Sean N. Parker Center for Allergy and Asthma Research and Before Brands, Inc., outlined the development of a 16-allergen mixture and described the rationale and design of the INTENT study, which will evaluate the potential benefits of this product to support early food allergen introduction. The symposium concluded with a live question and answer session.

Welcome and Introduction

Angela Claver Monzón

Food allergies are a growing health epidemic, with population-based surveys in the USA estimating that up to 8% of children and 11% of adults are now living with a food allergy.[1,2] During the 1990s and early 2000s, international guidelines recommended the avoidance of commonly problematic food during infancy due to the belief that early introduction of these foods may increase the risk of allergies. However, beginning with the publication of the LEAP trial in 2015,[3] a paradigm shift in the understanding of food allergy prevention has occurred. Clinical guidelines now generally recommend the introduction of potentially allergenic food after 4–6 months of exclusive breastfeeding.[4-6]

Real-World Experience in Early Food Allergen Introduction

Andrea Mikkelsen

Food allergies are one of the most common chronic diseases in early childhood,[7-9] requiring clinicians and dieticians to commit considerable time to their prevention, diagnosis, and management. For babies, the transition from breast or bottle feeding to eating solid food can be challenging and requires learning a completely different feeding technique. Mikkelsen highlighted that infants typically triple their birth weight during the first year of life and then further double their weight by the age of 6 years. During this time, children must develop good eating skills and consume a diverse and nutritious diet to support growth and prevent disease. For this reason, there are guidelines to support infant feeding, which all now recommend early rather than the delayed introduction of food allergens to prevent food allergies.[4-6]

The importance of the early introduction of food allergens is supported by data from a recently published study, which randomised infants (n=2,397) from a general population into a food intervention group (early complementary feeding of peanut, cow's milk, wheat, and egg from 3 months of age); a skin intervention group (skin emollients from age 2 weeks–<9 months); a combined intervention group (food and skin interventions); or to a no intervention group.[10] In this study, food allergies at 36 months of age were diagnosed in 0.9% of infants in the food intervention group and 1.2% of the combined intervention group, compared with 3.0% of the skin intervention group and 2.3% of the non-intervention group.[10] Overall, there was a significant reduction in the prevalence of food allergy in the food intervention group compared with the no food intervention group (risk difference: -1.6% [95% confidence interval: -2.7–-0.5]; odds ratio: 0.4 [95% confidence interval: 0.2–0.8]).[10] Mikkelsen emphasised the importance of this study of infants from a general population, as food allergies often develop in children without known genetic risk factors for food allergies. Mikkelsen also highlighted the importance of diet diversity to prevent food allergies,[4,11-13] including a recently published study by

Venter et al.,[14] which demonstrated that consuming vegetables and yoghurt during pregnancy could reduce the risk of any allergy in offspring.

Mikkelsen also raised the issue of reduced diet diversity and dysbiosis, which is a microbial imbalance in the gut.[15] In addition to food allergies, dysbiosis can result in other inflammatory conditions, including skin conditions, inflammatory bowel diseases, functional gastrointestinal disorders, and neuropsychiatric disorders.[16] The gut microbiota may play a protective role throughout life and not just in infancy and childhood. This is illustrated by a study in twins, which demonstrated significant differences in fecal microbiomes and metabolomes in twin pairs throughout adulthood.[17]

Mikkelsen acknowledged that the early introduction of food allergens can be challenging for infants, caregivers, and clinicians.[18-22] It is important to note that parents and caregivers were typically born and raised when food avoidance was recommended. As a result, the knowledge and experience of infant caregivers are now being challenged, and their acceptance of the new guidance may require significant education and support. The impact of these challenges is illustrated by a recent survey in the UK, which showed that many caregivers continue to delay the introduction of food allergens to their infants beyond 6 months of age (Nestlé Health Science, unpublished data). It was noted that dairy and oats are typical weaning foods and are hard to avoid; however, the introduction of other food allergens typically requires an active decision to be made.

Mikkelsen also reflected on the large quantity of typical food allergens that need to be consumed to provide 4 g of protein. This can be quite a considerable amount for infants, particularly given that they have other dietary requirements to fulfil, including the consumption of fruits, vegetables, and cereals. Mikkelsen emphasised the importance of practical nutritional counselling, and highlighted that dieticians can not only help with the prevention and management of food allergies, but can also help families when the allergy is outgrown. For example, many families continue to avoid certain foods despite clinicians' advice to reintroduce these foods. Although there can be a reluctance to introduce food allergens into the diets of infants and children, Mikkelsen highlighted that this could be overcome. A good example of encouraging early introduction can be seen in the EarlyNuts study,[23] which reported that peanuts and eggs were introduced into the diet of over 80% of 12-month-old children after the Australian infant feeding guidelines were updated in 2017.[23]

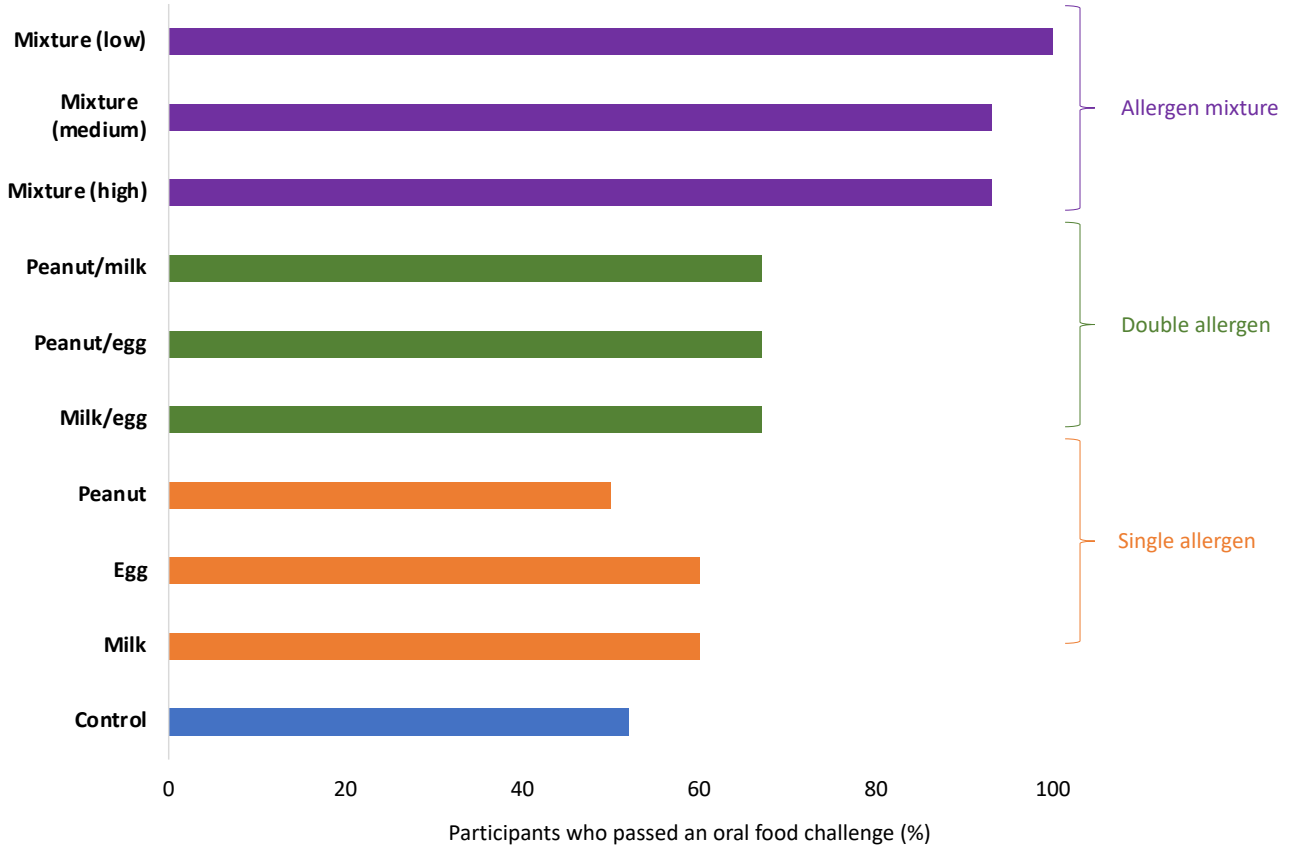
It was noted that although a vegetarian diet can provide sufficient nutrition and diet diversity, parents do require a considerable amount of knowledge and planning to ensure that children receive a well-balanced vegetarian or vegan diet.[24] Mikkelsen highlighted that growing children have much higher nutritional needs than adults and that an inflammatory state can also lead to higher energy and nutrient needs. She emphasised that in any avoidance diet, it is important to focus on what is being substituted for the avoided foods. Although it is easy to obtain advice on what foods to avoid, there is a lack of available information on what to substitute these with. It is also important to ensure that families are aware that there are additional benefits to a diverse diet for the prevention and/or management of many current diseases, including cardiovascular disease,[25] obesity,[26] Type 2 diabetes,[27,28] certain types of cancer,[29,30] and infectious diseases.[31] Mikkelsen concluded that as we now enter the era of encouraging a broad diet for infants, it is more important than ever to provide nutritional support and guidance to their families.

Early Introduction of a Multi-allergen Mixture for Prevention of Food Allergy: A Pilot Study

Kari Nadeau

Nadeau began by emphasising the importance of ensuring that children receive a wide variety of proteins, vitamins, and textures in their diet so that they can live without fear of eating. She also highlighted the increasing body of evidence

Figure 1: Results of an oral food challenge in infants who received a single, double, or 10-allergen mixture of food allergens for 1 year.



that feeding a diverse range of multiple common food allergens early and frequently may reduce the risk of developing food allergies.[3,11,32] In particular, it was noted that larger quantities of food allergens may not be required, with a recent study by Nishimura et al.[33] demonstrating that consumption of small amounts of allergens can be sufficient to reduce the incidence of food allergies. Despite this growing evidence and recent guideline changes, the introduction of multiple food allergens to infants can be difficult to manage and there is a clear, unmet need to develop methods for introducing potential dietary food allergens that are both tolerable to children and convenient and practical for caregivers.

In this presentation, Nadeau described the results from a 1-year randomised, unblinded, prospective, descriptive pilot study (NCT04828603),[34] which was designed to evaluate the safety and efficacy of three methods for the early introduction of food allergens.[35] The study enrolled infants between 2 and 12 months of age, with approximately 50% of infants considered to be at high risk of atopy (defined as having either one first-degree relative with a food allergy or atopic dermatitis or two first-degree relatives with atopic disease). Infants with any chronic disease, any known genetic disease, or a known food allergy were excluded. Of the 180 infants enrolled, 51% were female and the median age was 6 months. The majority (51%) were Caucasian, with the remainder being either Asian (20%), African American (14%), or Hispanic (11%). Most participants (83%) had eczema, with 46%, 25%, and 12% described as having mild, moderate, or severe eczema, respectively.

The participants were randomised into 10 groups with stratification according to the risk of atopy. Participants received either a single food allergen (egg, milk, or peanut; n=15 each), a double food allergen (peanut and milk,

peanut and egg, or milk and egg; n=15 each), or a 10-allergen mixture (comprising almonds, cashew, egg, hazelnut, milk, peanut, salmon, shrimp, walnut, and wheat) daily for 1 year. The 10-allergen mixture was given at either a low (300 mg/day; 30 mg of each allergen; n=15), medium (900 mg/day; 90 mg of each allergen; n=15), or high (3,000 mg/day; 300 mg of each allergen; n=15) serving size. The final group included 45 age- and sex-matched controls who avoided all potentially allergenic foods for the duration of the study. No increases in allergic reactions were reported regardless of risk stratification and baseline eczema status following the introduction of single, double, or a mixture of allergens, indicating that this approach is likely safe up to a serving size of 3,000 mg of protein.

Only half of the participants in the control arm (52%) passed an oral food challenge that was performed 2–4 years after the start of the study. In contrast, almost all participants (93–100%) who received the 10-allergen mixture passed (realitve quality factor: <0.01 for all dose groups versus controls; Figure 1). No significant differences compared with the control group were observed for any of the single or double food allergen subgroups.

A food diary completed at the end of the study revealed that only 16% of infants in the control group were eating more than 10 foods as table foods by 1 year of age. This increased to 53–67% and 53–73% for infants who received one and two food allergens, respectively, and 93–100% for infants who received the 10-allergen mixture (Figure 2).

Allergen-specific IgE and IgG4 levels were measured in blood samples collected from all participants at baseline and the end of the study. Peanut-specific IgG4/IgE ratios increased from baseline to the end of the study for all groups who consumed peanut allergen during the study, but not in the groups that did not consume peanut (Figure 3). Of note, a greater increase in this ratio was observed in the participants who consumed the 10-allergen mixture compared with those who consumed peanut allergen in the single or double allergen groups. Nadeau explained that this might indicate that the immunological response to a larger mixture of proteins may differ from that achieved with only one or two allergens. However, the reasons for this are currently unclear. Similar results were also observed for the milk-specific and cashew-specific IgG4/IgE ratios, with specificity

Figure 2: Percentage of infants eating more than 10 food items as table foods by 1 year of age.

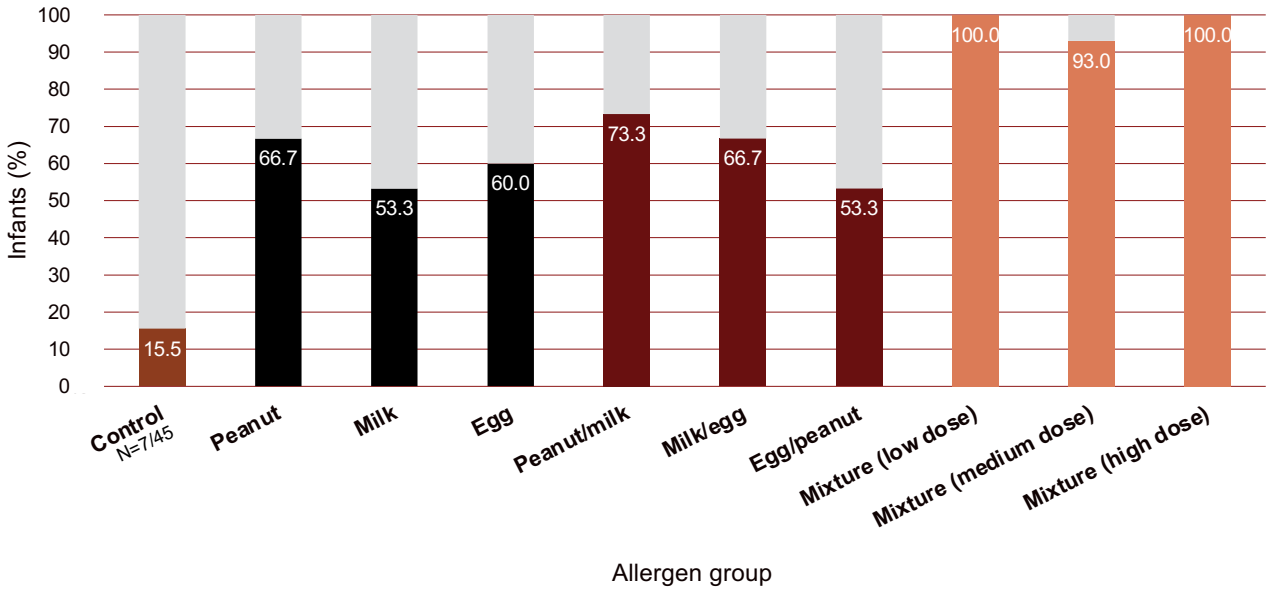
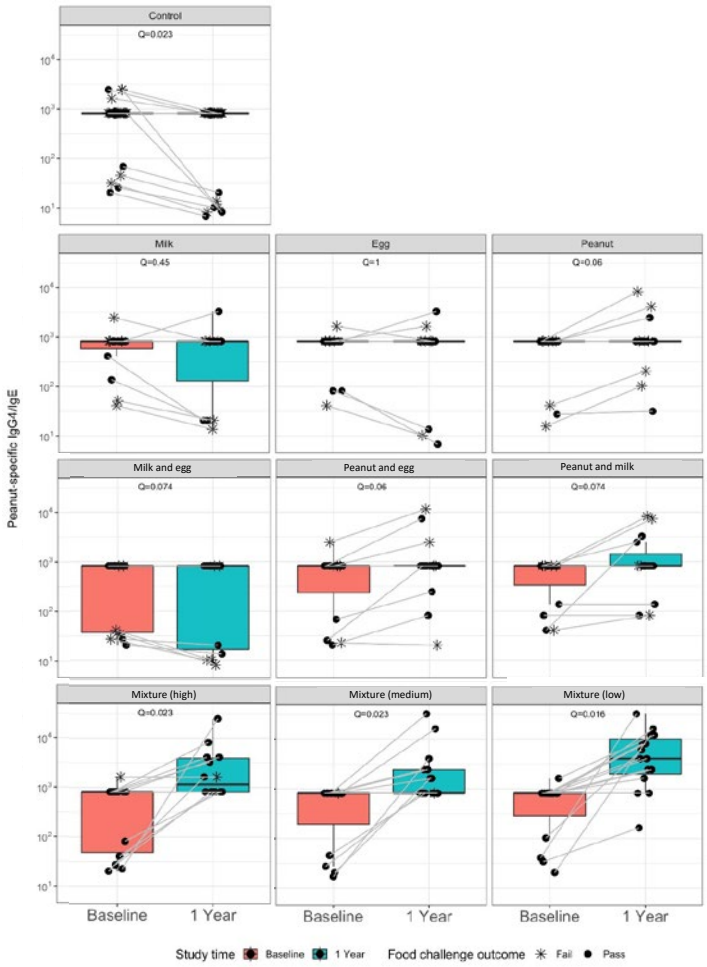


Figure 3: Peanut-specific IgG4/IgE ratios for the control, single, double, and multi-allergen groups at baseline and after one year from the start of the study.



Adapted from Quake et al.[35]

only demonstrated for milk and cashew-containing foods, respectively. Nadeau also drew attention to the results from the control group. For these participants, the IgG4/IgE ratio is not stable but instead declines over time. Similar results have been observed in the control groups of other early introduction randomised controlled trials, indicating that the risk of developing food allergies may increase for infants who are not engaged with the early introduction of food allergens. It is also interesting to note that the increases in the IgG4/IgE ratio are driven by increases in IgG4 rather than decreases in IgE. This may be indicative of an increase in tolerance to these foods.

Nadeau concluded that there was an improvement in food tolerance across all active groups, with the percentage of participants able to consume up to 8 g of protein being significantly higher in groups receiving a 10-allergen mixture, regardless of serving size, compared with a control group. Consistent with this, biomarker analysis identified a trend for immune protection and loss of allergic mechanisms in patients receiving the 10-allergen mixture. Importantly, there was no increase in the incidence of eczema, even in patients who had eczema at enrolment or who were considered at high risk of atopy. In addition, infants who received the 10-allergen mixture were more likely to diversify their diet compared with participants in the control group or those receiving single or double allergens.

In summary, the results of this pilot study indicate that daily dosing of a small number of mixed food proteins may be a convenient, safe, and effective method for preventing food allergies in infants. Further research will be required to determine the serving size, frequency, and time to start early infant feeding that optimises tolerability and reduction in allergy risk. This should ideally be performed using randomised, prospective studies rather than performing retrospective, sensitivity analyses that extrapolate backwards using statistical modelling.

Early Data from the INTENT Study: Evaluating a Daily Multi-allergen Mixture

Wendy Sue Swanson

Swanson began by outlining how infant feeding guidelines have dramatically changed following the publication of the LEAP and EAT trial studies in 2015 and 2016, respectively.[3,31] In 2017, the American Academy of Pediatrics (AAP) reversed its earlier guidance and endorsed the recommendations from the National Institute of Allergy and Infectious Diseases (NIAID) for an early introduction of peanut protein for infants who are at increased risk of developing a peanut allergy.[36] In the same year, the U.S. Food and Drug Administration (FDA) released a qualified health claim stating that introducing food containing ground peanuts to infants with severe eczema and/or an egg allergy may reduce the risk of developing a peanut allergy by 5 years of age.[37] In 2020, the American Academy of Allergy, Asthma and Immunology (AAAAI); the American College of Allergy, Asthma and Immunology (ACAAI); and the Canadian Society of Allergy and Clinical Immunology (CSACI) produced consensus guidelines stating that infants should be fed all common allergens from 4–6 months of age when solids are introduced.[4] Subsequently, recent research has demonstrated that consuming even small amounts of multiple food allergens may be an effective strategy to lower the risk of food allergy development.[33,35]

Swanson proceeded to describe the development of the SpoonfulONE (Nestlé, Vevey, Switzerland) product, which contains a blend of 16 common allergens (30 mg each of almond, cashew, cod, egg, pecan, pistachio, salmon, sesame, hazelnut, milk, oat, peanut, shrimp, soy, walnut, and wheat). This product was developed based on findings from a 1-year feeding study in infants and children, which showed that consumption of a protein mixture with 10 foods was superior to consumption of single or double allergens at reducing levels of food-specific IgE, with 30 mg and 300 mg portions sizes being similarly effective.[38] The safety of this product was evaluated in the I'm Eating Study (NCT03667118),[39] which randomised 705 healthy infants aged 5–11 months to receive either the multi-allergen product or placebo daily for 28 days.[40] Caregivers reported any symptoms that occurred in the 2 hours following consumption of the product or placebo each day. Overall, there was no significant difference between the product and placebo groups in the proportion of infants with any caregiver-reported symptoms.[40]

This product is currently being evaluated in the INTENT study (NCT04803981),[41] a controlled, open-label, pragmatic, direct-to-participant trial that randomised healthy infants aged 4–6 months to receive either a standard diet alone or a standard diet plus a daily serving of the multi-allergen product. Infants with gastro-oesophageal reflux disease or with clinician-diagnosed food allergies were excluded. All data are caregiver-reported and collected directly from a mobile application platform (app). For the 18-month trial, all caregivers will complete monthly e-questionnaires on diet diversity and the age at which nine common foods (peanut, milk, cashew, egg, cod, shrimp, wheat, soy, and sesame) are introduced. For the active group, daily electronic online questionnaires to assess compliance and quarterly e-questionnaires on parental comfort with introducing food proteins and the convenience of long-term multi-food allergen product use will also be completed. The primary endpoint is the proportion of children able to tolerate five common foods (peanut, egg, cashew, cod, and sesame) in two feedings after 12 months in the study. Secondary endpoints include parental comfort with using this product and ease of use, diet diversity, and ability to tolerate nine common foods at 18 months. Safety will be evaluated via the collection of adverse events related to allergic reactions. Eczema and other symptoms of IgE-mediated allergic reactions will be considered adverse events of special interest.

Recruitment was potentially challenging due to the COVID-19 pandemic and the narrow window of eligibility in an infant's life (eligibility was only when infants were between 4 and 6 months of age). However, online recruitment strategies have been successful, with approximately 75% of participants recruited via emails sent to parents who were members of the BabyCenter (San Francisco, California, USA) online parenting forum. Additional participants were recruited via social media or in-clinic advertisements. In total, 496 infants with eczema were recruited and stratified based on the severity of their eczema using the Patient-Oriented Eczema Measure (POEM) scale. A further 1,207 infants without eczema have also been recruited. The findings from the INTENT study may provide valuable information on the introduction of food allergens and serve as a blueprint for future large-scale, digital studies that evaluate strategies for the early introduction of infant food allergens.

Live Question and Answer Session

Angela Claver Monzón, Andrea Mikkelsen, and Wendy Sue Swanson

The session concluded with a live question and answer session. Monzón reiterated that many paediatricians and families still believe that certain foods should be avoided in infancy and that this belief may lead to ongoing problems with food allergies in the future. The key to improving this situation will be to teach appropriate strategies for early food introduction to healthcare professionals who work with children.

Swanson clarified that the patients in the control arm in INTENT are not receiving a placebo treatment but are real-world controls. They will continue to be followed up throughout the trial via the mobile app, with their caregivers continuing to complete surveys prompted by reminders sent through the app. Caregivers will also receive a small fee for completing each survey as motivation to participate. Both groups in the study will have access to standard educational resources via the app. Swanson also confirmed that the product used in INTENT only contains food items and not any other supplement or non-food items. She agreed that infants may benefit from exposure to allergens beyond food (e.g., pollen and mites) but that this can be achieved by taking babies outside. Swanson also stated that she would be happy to share the educational resources used for the INTENT app with other researchers, and that she will be presenting a video tutorial to demonstrate the function of the app at a separate European Academy of Allergy and Clinical Immunology (EAACI) session.

Monzón noted that differences exist between countries in their approach to preventing food allergies. She highlighted that it is important for all countries to inform parents and other paediatricians of the findings from recent studies. Swanson added that, in the USA, she is involved with events that provide information for new parents, including an update on the latest data that support early allergen feeding for infants. Educational sessions on infant feeding are also included at several academic meetings, including the AAP meeting. Information is also available in paediatric journals to ensure that paediatricians are aware of the most recent data that support the need for regular exposure to allergens to induce and maintain immunological tolerance.

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Hereditary Angioedema Management: From Dealing to Leading

This two-part digital symposium series sponsored by CSL Behring, took place on 1st and 2nd July 2022, as part of the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress, held in Prague, Czechia

Chairpersons:

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Speakers (Symposium 1):
Speakers (Symposium 2):

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Disclosure:

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Meeting Summary

A two-part digital symposium series entitled 'Hereditary Angioedema (HAE) Management: From Dealing to Leading,' took place during the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress, held in Prague, Czechia, in July 2022. The first symposium, 'The Journey Towards Disease Control in HAE', held on 1st July 2022, was chaired by Markus Magerl, Department of Dermatology and Allergy, Charite Universitätsmedizin, Berlin, Germany. Speakers Grzegorz Porębski, Department of Clinical and Environmental Allergology, Jagiellonian University Medical College, Kraków, Poland, and Mauro Cancian, Department of Systems Medicine, University of Padova, Italy, discussed how the advent of new disease-specific HAE treatments have contributed to the evolution of the HAE management guidelines, and the resulting impact on the lives of patients with HAE. The latest international management guidelines from the World Allergy Organization (WAO)/EAACI newly define the goals of treatment in HAE as achieving total control of the disease and normalising patients' lives, stressing that this can currently only be achieved by long-term prophylactic (LTP) treatment. The second symposium, 'Making the Goals of HAE Management Achievable with Subcutaneous C1-Inhibitor', held on 2nd July 2022, was chaired by Pavlína Králíčková, Department of Clinical Immunology and Allergology, University Hospital Hradec Králové, Czechia, who also provided a brief overview of the development of the subcutaneous formulation of C1-inhibitor for LTP. Emel Aygören-Pürsün, Angioedema Clinic and Center for Hereditary Angioedema, University Hospital Frankfurt, Goethe University, Germany, and Teresa Caballero, Allergy Department, Hospital Universitario La Paz, Madrid, Spain, then used case studies to highlight the necessity of assessing and monitoring a patient's disease activity, the associated quality of life, and disease control to allow for possible adaptations to the treatment plan. Both speakers also highlighted how the use of subcutaneous C1-inhibitor for LTP can contribute towards the achievement of the goals of HAE treatment, namely achieving total disease control and normalising patients' lives.

INTRODUCTION

Hereditary angioedema (HAE) is a rare genetic disease that manifests as recurrent cutaneous or submucosal oedema, most commonly affecting the skin, the abdomen, and upper respiratory tract.[1] Pain, disfigurement, nausea, and fatigue can all be experienced during an HAE attack,[2-4] with manifestation, frequency, and severity varying both between patients and within the same patient, making HAE an unpredictable condition.[1] The unpredictability of HAE can cause substantial physical and emotional impairment, at the time of an attack but also between attacks, potentially due to the continuous fear of attacks, the need to avoid triggers of attacks, the psychological distress due to the chronic disease burden, and the presence of comorbid diseases such as depression and anxiety.[3,5-7]

HAE has an estimated prevalence of 1:50,000 in the population with onset of symptoms typically occurring in childhood or adolescence.[1] HAE Type 1 and 2 are caused by mutations in the gene *SERPING1,* which codes for the serine protease C1-esterase inhibitor (C1-INH).[8] In patients with HAE Type 1, both C1-INH protein levels and function are low; in those with HAE Type 2, C1-INH protein levels are either normal or elevated but C1-INH function is low.[1]

C1-INH acts as the major inhibitor of the complement proteases C1r and C1s and mannose-binding lectin-associated serine proteases (MASP) 1 and 2, as well as the contact-system proteases plasma kallikrein and coagulation factor XIIa. Additionally, C1-INH plays a minor role in the inhibition of plasmin and factor XIa in the fibrinolytic and coagulation systems, respectively. In the absence of sufficient functional C1-INH levels, the activation of these target proteases is enhanced. In HAE Types 1 and 2, the deficiency of functional C1-INH leads to uncontrolled activation of plasma kallikrein and FXII, in turn leading to the overproduction of bradykinin, which, upon binding to the bradykinin B2 receptor, results in increased vascular permeability and swelling.[1,9,10]

SYMPOSIUM 1: THE JOURNEY TOWARDS DISEASE CONTROL IN HEREDITARY ANGIOEDEMA

Day 1 of the two-day symposium series focused on the goals of treatment in HAE. Porębski presented a talk entitled 'HAE Then and Now: Evolving Treatment Goals', in which he summarised the important milestones in the development of HAE management guidelines and highlighted the new treatment goals. Cancian then followed with a discussion on the 'Impact of the New HAE Guidelines on Patients', to demonstrate the practical implications for patients resulting from the implementation of treatment guidelines in daily practice.

To establish how the management guidelines of HAE have evolved over time due to the availability of new therapeutic options, Porębski and Cancian both provided an overview of the milestones in the treatment of HAE. The treatment of HAE Types 1 and 2 is based on three pillars: on-demand or acute treatment (aiming to control HAE attacks when they occur); short-term prophylaxis ([STP]; aiming to prevent HAE attacks during exposure situations with an increased risk of an attack, including preprocedural prophylaxis); and long-term prophylaxis ([LTP]; routine treatment to reduce the burden of HAE by preventing attacks).[1] As stressed by Cancian, these treatment modalities "should not be regarded as mutually exclusive, but rather as additional opportunities to be used in the same patient." Whereas attenuated androgens, antifibrinolytics, and fresh frozen plasma were being used for the management of HAE in the 1960s, the discovery of the role of C1-INH and bradykinin in the pathogenesis of HAE opened the way for disease-specific treatments targeting different levels within the contact system. While the 1970s saw the introduction of purified plasma-derived C1-INH replacement therapy, the first consensus algorithms for HAE management did not appear until 2004.[2,11] Additional disease-specific treatments with novel mechanisms of action were introduced early in the 21st century for the treatment of acute HAE attacks, including recombinant C1-INH, bradykinin antagonist icatibant, and kallikrein inhibitor ecallantide, leading to corresponding updates in consensus treatment algorithms.[12] During the last decade, a number of highly effective and safe disease-specific treatment options for LTP, including intravenous (IV) and subcutaneous (SC) C1-INH and the kallikrein inhibitors lanadelumab and berotralstat, have further contributed to the advancement of the HAE management guidelines.[1,13,14]

The 2021 revision and update of the WAO/EAACI guideline for the management of HAE was developed with the contribution of international experts (including clinicians, scientists, patients with HAE, and patient advocates) from different countries spanning five continents, using the Delphi method. Porębski highlighted the main changes that have been implemented, the most important of which is the inclusion of the newly defined ultimate goals for the treatment of HAE: achieving total control of the disease and normalising patients' lives.[1] Providing additional insight into the ultimate goals, the guideline clarifies that they essentially translate to patients no longer having attacks, which can currently "only be achieved by LTP treatment." The recommended first-line treatment options for LTP now include SC and IV plasma-derived

C1-INH, lanadelumab, and berotralstat, and it is the availability of these modern treatment options of personalised disease management, and of new tools for measuring treatment outcomes that make achieving complete control of HAE a realistic possibility for many patients.[1]

Over the years, new evidence on the burden of HAE, and heightened physician awareness of the burden, had implications on the treatment goals in HAE, especially with respect to LTP. Porębski presented his personal experience from a study conducted in 2009, in which >50% of patients reported moderate-to-extreme impact of HAE on many aspects of their lives including travel plans, free time, concern about their appearance, social life, and a sense of responsibility about transmitting HAE to any offspring.[15] The understanding that the impact of HAE is much more than just the attacks experienced brought with it a greater understanding of the importance of LTP and an evolution in the criteria for initiating LTP. There is now agreement that the decision to start a patient on LTP should not be based on attack frequency and severity alone, but should be individualised taking into consideration disease activity, burden, and control, as well as the patient's preference.[1,16] Access to urgent care and the benefit–risk profile and treatment burden of available acute and prophylaxis therapies are also factors to consider.[16] Importantly, initiation of LTP should be a joint decision between the patient and clinician[17] and evaluation of the need for LTP should be carried out at each clinic visit.[1]

Porębski also highlighted the update that was made in the recommendation for STP; whereas previously STP had been recommended before procedures that can induce an attack, the new guideline now also suggests considering STP prior to exposure to patient-specific angioedema-inducing situations.[1] The WAO/EAACI 2021 guideline-recommended HAE treatments within each treatment setting are illustrated in Table 1.

Important considerations for the future, as highlighted by Porębski, include determining whether STP should be handled differently in patients with a complete response to LTP, and whether patients initiated on LTP should continue for the duration of their lives. Additionally, knowing that treatment responses vary between individual patients, the possibility of identifying the best responders in advance would be advantageous for the implementation of precision medicine to match patients to the therapies most appropriate for them.[18,19] With respect to future treatments, Porębski highlighted that 10 of the current 12 investigational drugs for HAE are being investigated for use in LTP, which aligns with the new treatment goals as defined in the 2021 WAO/EAACI guideline.[1,20]

Cancian then elaborated on the impact of the new guidelines on patients, stressing that the new goals of treatment reflect a changing treatment paradigm and the vast progress that has been made compared to the earliest consensus algorithms and guidelines: within the last two decades, the aim of treatment in HAE has moved significantly beyond just reducing the risk of mortality from acute attacks to also encompass reducing the overall burden of the disease on patients. Burden of disease is also relevant for paediatric patients and their parents, and specialised guidelines for paediatric patients have now been developed.[21]

Discussing the heightened awareness around the burden of HAE, Cancian underscored the importance of the patient-reported outcome measures (PRO) that have been validated in recent years to better understand the global burden of angioedema from the patient's perspective. There is now consensus agreement among the HAE community that patients with HAE should provide input on how they or their treating physicians assess whether HAE is controlled or their life is normalised.[17] For the first time, the 2021 WAO/EAACI guideline puts particular emphasis on the importance of patients monitoring their disease activity, impact, and control to optimise treatment, particularly in patients who are using LTP.[1] As detailed in Table 2, there are a number of generic and HAE-specific tools that can help with this.[6] Cancian particularly emphasised the attention that has been given to the development of questionnaires to assess the quality of life (QoL) of patients. Giving his own personal experience, he mentioned that in the past his patients would be asked to document their attack frequency, location, and whether the attacks had been treated, but only to prescribe new medication. In current practice, time is taken to have qualitative discussions with patients to understand how they feel in general and whether their current therapy is effectively reducing the burden of disease and improving QoL.

Table 1: Treatment for hereditary angioedema according to WAO/EAACI 2021 guidelines.[1]*

Treatment	Acute	STP/ preprocedural prophylaxis	LTP
pdC1-INH (IV)	✓✓	✓✓	✓✓†‡
pdC1-INH (SC)	N/A	N/A	✓✓‡
rhC1-INH (IV)	✓✓	✓§	N/A
Icatibant	✓✓	N/A	N/A
Ecallantide††	✓✓	N/A	N/A
SDT plasma	✓	N/A	N/A
Fresh frozen plasma	✓	✓	N/A
Attenuated androgens	N/A	✓	✓
Antifibrinolytics	N/A	✓**	N/A
Lanadelumab	N/A	N/A	✓✓‡
Berotralstat	N/A	N/A	✓✓‡

*Guideline recommendations may vary from the approved product indications across different countries. ✓✓ indicates the first-line recommendations; ✓ indicates alternative treatment options when first-line options are not available; † indication for use varies by manufacturer; ‡ in patients ≥6 years old; ‡ in patients ≥12 years old; § could be considered if IV pdC1-INH is not available; ** not recommended by most guideline experts; †† currently approved in the USA only.

EAACI: European Academy of Allergy and Clinical Immunology; IV: intravenous; LTP: long-term prophylaxis; N/A: not applicable; pdC1-INH: plasma-derived C1-inhibitor; rhC1-INH: recombinant human C1-inhibitor; SC: subcutaneous; SDT: solvent detergent-treated; STP: short-term prophylaxis; WAO: World Allergy Organization.

Cancian stressed that real-world application of guidelines is not always easy, particularly in rare diseases. It necessitates close collaboration between reference centres, clinical and scientific networks, patient associations, single physicians, and their patients. Of note, disparities in healthcare resources for the management of HAE among different countries also still need to be resolved.[30]

In the closing discussion of the symposium, the speakers addressed key questions and firstly focused on how often a patient's progress should be monitored using PROs. There was agreement that this should generally be done at each visit, but individualisation is also needed based on disease severity. Magerl mentioned that, particularly when there is a change to a treatment plan, it may be necessary to monitor more frequently.

With regard to the integration of the guidelines into daily practice, Porębski stressed the importance of maintaining close collaboration with patients and of increasing their awareness of the guidelines, ensuring patients know the implications for their treatment and QoL.

The issue of how long a patient should remain on LTP was discussed, with Cancian suggesting that, given that patient phenotype changes over time, following the first year, LTP could be periodically suspended to ascertain if it is still needed, again using an individualised approach. Porębski commented that the best situation would be to eventually have a biomarker.

Table 2: Patient-reported outcome measures in hereditary angioedema.

Outcome assessments	Aspect of HAE assessed
Angioedema Activity Score (AAS) [22]	Disease activity
HAE Activity Score (HAE-AS)[23]	Disease activity
Angioedema Control Test (AECT)[24]	Disease control
36-item Short-Form Health Survey (SF-36)[25]	Quality of life/disease burden
EuroQoL 5-Dimensions Survey (EQ-5D)[26]	Quality of life/disease burden
Angioedema Quality of Life (AE-QoL) questionnaire[27]	Quality of life/disease burden
US Angioedema Association Quality of Life survey (HAEA-QoL)[28]	Quality of life/disease burden
HAE-Quality of life (HAE-QoL) questionnaire[29]	Quality of life/disease burden

HAE: hereditary angioedema.

SYMPOSIUM 2: MAKING THE GOALS OF HEREDITARY ANGIOEDEMA MANAGEMENT ACHIEVABLE WITH SUBCUTANEOUS C1-ESTERASE INHIBITOR

The second day of the symposium series looked at how SC C1-INH, as a new LTP option, can help clinicians and patients achieve total disease control and normalisation of patients' lives. Králíčková opened with a brief introduction to SC C1-INH, followed by Aygören-Pürsün who explained the multi-dimensional impairment that patients with HAE experience in her presentation 'Managing HAE: More Than Just Treating Attacks'. Caballero then discussed 'Optimising Long-Term Prophylaxis: Treating-to-Target Made Possible', focusing on the need for continuous reassessment of patients' treatment plans in order to determine the extent to which the treatment goals are being achieved and to make adjustments as appropriate. Aygören-Pürsün and Caballero presented examples of their own patient cases to demonstrate how SC C1-INH can help patients achieve adequate disease control, improving patients' QoL and enabling them to live normal lives.

Regular IV C1-INH replacement, administered twice weekly, has been shown to be an effective treatment option for LTP with an acceptable safety profile, and has thus had a first-line recommendation in HAE management guidelines for several years. To overcome the administration burden associated with twice weekly regular IV infusions, a SC C1-INH formulation for LTP was developed.[31] The SC route can provide greater convenience in administration as well improved steady-state plasma concentrations of C1-INH compared with LTP with IV C1-INH, thus allowing for better symptom control.[1,32,33] Králíčková highlighted results from the randomised, double-blind, placebo-controlled Phase III study of SC C1-INH (COMPACT), in which the 60 IU/kg twice weekly dose of SC C1-INH led to a 95% median reduction in attacks versus placebo and a 100% median reduction in the use of rescue medication.[31] In the open-label, parallel-arm extension study of COMPACT, patients receiving 60 IU/kg SC C1-INH (n=63) achieved a median annualised attack rate of 1.0 attack per year.[34] Králíčková further emphasised that these patients also experienced clinically meaningful and sustained improvements from baseline in overall QoL, anxiety, depression, productivity, and satisfaction with therapy.[35]

Adverse events with SC C1-INH were reported in similar proportions of patients as compared with placebo and predominantly included injection-site reactions, though these occurred at a low rate, were mild, and resolved within 24 hours. No anaphylactic reactions or neutralising antibodies to C1-INH were observed.[31,34] Studies in adolescent,[36] elderly,[37] and female[38] patients have demonstrated similar efficacy and tolerability.

Building upon the disease burden discussion of the first symposium, Aygören-Pürsün emphasised that the burden of HAE is not just the symptoms suffered during an attack. Patients experience multi-dimensional impairment in QoL, including comorbid anxiety and depression, time lost from social activities, school, and work, loss in productivity, and the burden placed on caregivers.[5-7] Patients' anxiety levels have been demonstrated to be in direct association with the level of pain experienced during their most recent attack.[5] Presenting data from a recent multinational patient survey examining the burden of illness in patients with HAE, Aygören-Pürsün explained that attack frequency and the severity of anxiety and depression are determinants of QoL and disease control for patients with HAE. As a result of the frequency of their attacks as well as their anxiety and depression severity, the majority of patients with HAE within the survey (82%) demonstrated poor disease control, with Angioedema Control Test (AECT) scores of <10.[3]

HAE can also potentially have a negative impact on educational and career opportunities of patients. Showing data from analyses performed in Europe, Aygören-Pürsün emphasised that patients miss an average of 20 days of school or work per year, and 45% of patients were absent from school or work during their last attack, which reaches 80% for a severe attack.[39,40]

Aygören-Pürsün went on to illustrate how the use of SC C1-INH can positively impact a patient's QoL, by presenting the case of a 41-year-old female patient with comorbid anxiety disorder and autoimmune thyroiditis. The patient's initial treatment was on-demand only, with IV C1-INH or SC icatibant; however, the patient experienced uncontrolled disease (rated by the AECT), attacks every 2–4 days, and other effects to their general health and QoL. Though initially reluctant to use LTP, the patient was prescribed SC C1-INH when they were 39-years-old, taking into account both their attack frequency and anxiety regarding the attacks. Though they did have some mild attacks during the initial transitional period and during a period of extreme stress related to personal circumstances, the patient experienced a 7-month long attack-free period. As Aygören-Pürsün underscored, the impact of the attack reduction was also reflected in the AECT measuring disease control which improved from 5 out of 16 (poor control) to 15 out of 16 (nearly complete control). The patient also showed increased scores on both general health and QoL measures, including diminished attack-induced anxiety.

Reflecting on this case example, Aygören-Pürsün shared how her patient's experience also resonates with a recent survey of 14 patients in the USA that received LTP with SC C1-INH for at least 3 months. Within this survey, patients reported improved QoL across multiple domains; importantly, patients reported no longer feeling limited by HAE and having less HAE-related anxiety and depression, expressing increased feelings of confidence, independence, optimism, and normalcy.[41] Aygören-Pürsün summarised the key implications for treatment decisions in clinical practice, reiterating that many patients with HAE, despite effective treatment of their attacks, continue to have multi-dimensional impairment in their QoL. Therefore, management of HAE should include regular assessment of QoL and disease control as the basis for treatment decisions.

The need for continuous monitoring of HAE disease activity, impact, and control was further underscored by Caballero as she presented a detailed case of a male paediatric patient and introduced the factors that should be considered when assessing whether a treatment plan is achieving disease control and normalisation of patients' lives. These factors enable a 'treat-to-target' approach for optimisation of HAE treatment and were agreed upon in the Delphi consensus process which led to the updated 2021 WAO/EAACI guideline (Table 3).[1,17]

The male patient was diagnosed aged 3 months during a family screening protocol, before they had exhibited angioedema symptoms. The treatment plan agreed at diagnosis was on-demand treatment and pre-procedural

prophylaxis, as needed, with IV pdC1-INH. Their first attack, at age 2 years, resulted in an emergency department visit. By age 11, the patient's disease activity had increased significantly and was having an impact on QoL. Both they and their parents missed time from school and work, respectively, and the patient received psychological support due to anxiety. The patient could not be autonomous or participate in sports, and teachers were concerned about their performance in school. The treatment plan was modified to receive SC icatibant for acute attacks, which they and their parents were trained to administer, with emergency department administration of IV pdC1-INH if required. They were also initiated on LTP with oral tranexamic acid.

Although at age 12 there was partial improvement in the patient's attack rate, there continued to be unmet needs: the patient was still not participating in sports or attending extracurricular activities, they were still receiving psychological support, and their parents were still missing workdays. The treatment plan was thus updated with a switch to LTP with self-administered SC C1-INH. Within the next year, the patient was attack-free and QoL improved substantially; they did not miss any school days, require any hospitalisations or emergency department visits due to HAE, and both they and their parents were very satisfied with the treatment.

This case, Caballero concluded, highlighted the particular needs of paediatric patients and their caregivers; HAE can impact a child's attendance and performance in school, potentially preventing future educational or career opportunities, and leads to anxiety for both the patient and caregivers.[40] The case also illustrated the importance of developing treatment plans in HAE based on a 'treat-to-target' approach. As such, treatment efficacy and safety, as well as the psychological impact of HAE, need to be regularly assessed and treatment plans adapted in order to achieve optimal results.[1,5] Caballero also emphasised that drug self-administration is feasible for young adolescents and that all patients should be trained to safely self-administer IV and SC therapies licensed for self-administration.[21]

In the closing remarks of the symposium, the speakers addressed key questions and discussed the advantages of SC C1-INH. Aygören-Pürsün remarked how SC C1-INH use by her patients has led to vast reductions in HAE attacks and long attack-free periods, giving patients more opportunity to live the life they always wanted

Table 3: Treating to target in hereditary angioedema. Consensus statements on the factors to consider when assessing disease control and normalisation of the patient's life.[17]

Factors to consider when assessing achievement of goals	Goal 1: Control of HAE agreement (%)	Goal 2: Normalisation of patient's life agreement (%)
Number of attacks experienced by a patient in a given time period	95	89
Proportional reduction in the number of attacks	95	84
Mean length of attack-free period	N/A	84
Requirement for rescue medication in a given time period	100	89
Number of ED visits or hospitalisations	95	95
Number of days of sick leave in a given time period	89	79
Number of hours of activity impairment in a given time period	84	84

ED: emergency department; HAE: hereditary angioedema; N/A: not applicable.

to live. With respect to monitoring progress after initiating LTP with SC C1-INH, Aygören-Pürsün also remarked that disease control and QoL questionnaires are completed by patients at every visit, so that a picture of their progress can be gained at the start of a consultation.

When discussing the treatment of adolescent patients, the importance of working with patients and their caregivers to ensure adherence to the treatment plan was emphasised, with Caballero remarking that using QoL instruments is particularly important to gain insight into specific problems the adolescent may be facing and to help individualise treatment.

Caballero also commented that she advises caregivers to help and encourage patients with HAE to try to live as normal a life as possible, not avoiding situations such as participating in sport due to fear of attacks, so that patients with HAE 'live as any other person'.

CONCLUSION

With the introduction of new therapeutic options and treatment modalities, HAE management has evolved from treating attacks with the aim of reducing mortality risk to preventing attacks with the aim of reducing QoL impairments. This is reflected in the most recently published 2021 WAO/EAACI HAE management guideline, where the ultimate goals of treatment have been defined as achieving total control of the disease and normalising patients' lives.

New options for long-term prophylaxis, such as SC C1-INH, together with personalised disease management that is optimised with the use of PROs, can ensure that patients are no longer just 'dealing' with their disease, but are instead 'leading' their disease to be able to live normal lives.

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Abstract Reviews

Introducing key insights into the latest research in the field of allergy and immunology, from abstracts presented at the European Academy of Allergy and Clinical Immunology (EAACI) 2022 Congress.

Does Variation in the Phage Communities of the Upper Respiratory System Exist?

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BACKGROUND

The human microbiome incorporates bacteria, archaea, fungi, viruses, and bacteriophages (phages).[1] Phages play a remarkable role concurrently as microbiome-regulating mediators and immune factors. This discovery enhances the proposition of a correlation between the reduction of their presence and the exacerbation of symptoms in patients with allergies or asthma.[2-5] This study has been conducted within the framework of a more extensive research project named CURE (Constructing a 'Eubiosis Reinstatement Therapy' for Asthma), which is dedicated to investigating the potency of phage therapy in patients with asthma. The present study examined intra- and interdaily fluctuations in the populations of *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* phages that colonise the human upper respiratory system.

MATERIALS AND METHODS

This study included 18 subjects of both sexes, aged 18–54 years. Half of the participants had nasopharyngeal swab specimens collected twice daily, and the other half three times a day. Samples were collected day-by-day for a total of 3 days. In the 135 samples that were taken, DNA isolation was performed using the NucleoSpin® Plasmid (Macherey–Nagel, Düren, Germany) kit. The detection of the phage genetic material was carried out using SYBR Green-based quantitative PCR. Statistical analysis of the results was performed with SPSS version 20 (IBM, Armonk, New York, USA) and STATGRAPHICS 19 (Statgraphic Technologies, Inc., The Plains, Virginia, USA) softwares.

RESULTS

M. catarrhalis phage population was observed more frequently in comparison with the other two examined species. This species was detected in 80% of the subjects both in the morning and at night. The variation of the phage population was estimated by means of simple regression analysis. The expression of *M. catarrhalis* and *S. aureus* phages appeared to be associated with time. While there was no intradaily variation, a progressively increasing interdaily trend was observed in *M. catarrhalis* phages, while the

S. aureus phage population seemed slightly reduced in the third night of the experiment. No significant alterations were observed in the *S. pneumoniae* phages.

DISCUSSION

Evidence suggests that phage populations tend to differentiate in relation to time. Considering this underlying correlation, this subject has the potential of further investigation, for the elucidation of all its aspects.

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Injection-Site Reactions Post-mRNA COVID-19 Vaccination

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BACKGROUND AND AIMS

Early studies have reported delayed injection-site reactions in up to 0.8% of individuals receiving Moderna messenger RNA (mRNA) vaccine.[1] These are believed to be benign and do not contraindicate subsequent doses.[2] Injection-site reactions after Pfizer-BioNTech mRNA vaccine have been less clearly described.[3] This study reports the characteristics of mRNA COVID-19 injection-site reactions post-Moderna and Pfizer-BioNTech vaccinations.

MATERIALS AND METHODS

Patients referred to the authors' dermatology service and allergy centre for reactions after COVID-19 vaccination between January 2021 and August 2021 were retrospectively reviewed. Inclusion criteria were adult patients who developed localised injection-site reactions after either Moderna or Pfizer-BioNTech mRNA vaccination. Patients with unrelated or non-injection site reactions were excluded. The data was analysed using IBM (Louisville, Kentucky, USA) SPSS Statistics version 22.0, with a p value of ≤0.05 being considered statistically significant.

RESULTS

Three hundred and twenty-two patients were referred for post-vaccination reactions, of which 21 developed injection-site reactions. Patients receiving Moderna mRNA vaccine had a longer median latency period (p=0.001), and were more likely to have a latency duration of >5 days (p=0.009). Secondary dissemination of the injection-site reaction was seen in both groups. More than half of these patients did not require any treatment. All 21 patients subsequently

received the second vaccine dose, of which two (9.5%) developed a mild recurrence of the reaction that did not require treatment.

CONCLUSION

Delayed local injection-site reactions to both vaccines appear to be benign. All patients went on to receive the second dose despite the initial first dose reactions, with none developing severe allergic reactions. While the latency between vaccination and onset of cutaneous lesions is significantly shorter following Pfizer-BioNTech vaccination, it remains unclear if pathogenic mechanisms behind injection reactions across the two vaccines differ. With the call for booster vaccinations globally, it is important to recognise that these reactions are mild, self-limiting, and should not deter one from subsequent vaccines. ●

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Epinephrine Auto-Injector Prescription and Use: A Retrospective Analysis and Clinical Risk Assessment of Adult Patients Sensitised to Lipid Transfer Protein

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Keywords: Anaphylaxis, epinephrine, follow-up, food allergy, lipid transfer protein allergy, panallergen.

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BACKGROUND

Lipid transfer proteins (LTPs) are allergens widespread in plant foods. They represent the main cause of food allergy in adults living in the Mediterranean Basin.[1,2] The manifestation and severity of LTP hypersensitivity are extremely variable. Given the peculiarities of this allergy and the unpredictability of its clinical manifestations, epinephrine auto-injector prescription and its actual use has become an important clinical issue.

AIMS

The purpose of this study was to investigate LTPs in patients, and the actual use of prescribed epinephrine auto-injector, as well as the appropriateness of its prescription according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines.[3]

In addition, the authors investigated the following in patients: (1) the occurrence of new food reactions in patients with a diagnosis of LTP allergy from at least 3 years prior; (2) the number of patients requiring access to emergency services; (3) presence of possible predictive factors to additional food reactions; and (4) patient adherence to annual follow-up visits.

MATERIALS AND METHODS

The present study was carried out on 165 adult subjects with at least a 3-year prior diagnosis of LTP allergy, presenting at the outpatient Allergy Unit of IRCCS Agostino Gemelli University Policlinic, Rome, Italy, between 1st January 2018 and 31st December 2020. All data were collected by medical records.

RESULTS

A total of 165 patients were included in the study, 110 females (66.7%) and 55 males (33.3%), with a mean age of 37.8±12.4 years. Epinephrine auto-injectors were prescribed in 108 patients (65.5%), in face of 67 (40.6%) patients having a strict indication to an ephinephrine autoinjector prescription. Based only on the clinical history, the authors recorded an epinephrine over-prescription of 25%. They monitored the onset of further reactions over the following 3 years of follow-up (Table 1), recording 68 new reactions during this time. In particular, they noted 33.8% (23 patients) had further reactions during the first year, 41.2% (28 patients) during the second year, and 25% (17 patients) during the third year. Most reactions (53/68; 77.9%) were characterised by local symptoms that promptly receded with home therapy (oral antihistamines and corticosteroid); systemic symptoms were recorded in 19.1% (13/68) cases, and 2.9% (2/68) of cases were anaphylactic. The patients rarely required an emergency department visit (16.1%), and only one patient (1.7%) used the epinephrine auto-injector whilst waiting for medical attention. Moreover, the authors observed an association between platanus pollen sensitisation (Pla a3) and severity of further reactions during the follow-up (p=0.026). Overall, 108 patients (65.5%) were lost during follow-up; 60 patients (35.7%) during the first year, 32 (19%) during the second year, and 16 (9.5%) during the third year. A large proportion of patients (86%) who attended the annual follow-up had an epinephrine auto-injector prescription. Logistic regression analysis revealed that five times more patients without epinephrine auto-injector prescription were lost, compared with patients with this prescription (p=<0.0005, hazard ratio: 5.08, 95% confidence interval: 2.2–11.7).

Table 1: Clinical severity and therapy of further reactions recorded during the follow-up.

		Year 1	Year 2	Year 3
Remaining patients at the beginning of the period		165	105	73
Lost patients (n; %)		60 (36.4%)	32 (19.4%)	16 (9.5%)
Further reactions (n; %)		23 (33.8%)	28 (41.2%)	17 (25.0%)
	Local symptoms (n; %)	16 (70.0%)	22 (79.0%)	15 (88.0%)
	Systemic reaction (n; %)	6 (26.0%)	5 (18.0%)	2 (12.0%)
	Anaphylaxis (n; %)	1 (4.0%)	1 (3.0%)	0 (0.0%)
Therapy				
	Home therapy (n; %)	16 (79.0%)	18 (82.0%)	10 (67.0%)
	Emergency department visit (n; %)	4 (17.0%)	6 (27.0%)	1 (6.0%)
	Use of ephinephrine auto-injector (n; %)	0 (0.0%)	1 (4.0%)	0
Percentages calculated on the basis of patients who remained in the follow-up				

CONCLUSIONS

The actual use of the epinephrine autoinjector alongside an incidence of severe allergic reactions seem be low in patients with LTP who had been previously diagnosed by an allergy unit. The relative epinephrine over-prescription rate could be justified by the peculiar and unpredictable features of this allergy. Further investigations would be useful to phenotype these patients, defining their risk profile and need for epinephrine autoinjector prescription, optimising individual treatment.

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Berotralstat for the Prophylaxis of Hereditary Angioedema: Outcomes in a Large Regional Immunology Centre in the UK

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BACKGROUND AND AIMS

Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic condition, whereby patients present with recurrent episodes of swelling. This affects the subcutaneous and submucosal tissues of the skin as well as mucous membranes such as the respiratory and gastrointestinal tracts.[1]

HAE is inherited in an autosomal dominant trend, which can be classified based on either the presence or absence of the levels (Type 1) or the function (Type 2) of the C1-esterase inhibitor, thus resulting in uncontrolled plasma kallikrein activity and an excess formation of bradykinin, a vasoactive peptide.[2,3]

Berotralstat is a highly selective oral kallikrein inhibitor used to treat both Type 1 and Type 2 HAE in patients aged ≥12 years. The efficiency and safety of the drug for prophylaxis of HAE have recently been established following clinical trials. It then became available in the UK via the Early Access to Medicine Scheme (EAMS) in November 2020.[4]

In this review, the authors compared their regional experience in using berotralstat since the EAMS was launched in November 2020 to the national survey that was presented

Table 1: Summary of Salford patients with hereditary angioedema who were commenced on berotralstat since the launch of the Early Access to Medicine Scheme (EAMS) in November 2020.

Gender	Age (years)	Diagnosis	Transitioned from other LTP, e.g., androgens	Adverse effects	Continued berotralstat
M	26	Hereditary angioedema Type 1	Not on LTP treatment	Mild headache stopped after a few days	Yes
M	45	Hereditary angioedema Type 1	Not on LTP treatment	None	Yes
M	54	Hereditary angioedema Type 1	Was on oxandrolone 2.5 mg	Unsatisfactory response to prevent HAE attacks	No
F	43	Hereditary angioedema Type 1	Was on oxandrolone 2.5 mg	None	Yes
F	71	Hereditary angioedema Type 1	Was on oxandrolone 2.5 mg	None	Yes
M	35	Hereditary angioedema Type 1	Was on oxandrolone 2.5 mg	Mild abdominal symptoms with a combination of cramps, nausea, diarrhoea, and vomiting	Yes
M	39	Hereditary angioedema Type 1	Was on oxandrolone 2.5 mg	Mild GI symptoms for a few days	Yes
F	27	Hereditary angioedema Type 1	Not on LTP treatment	Mild headache for a few days	Yes
M	24	Hereditary angioedema Type 1	Was on oxandrolone 2.5 mg	Unsatisfactory response to prevent HAE attacks	No
F	26	Hereditary angioedema Type 1	Not on LTP treatment	Mild headache for a few days	Yes

F: female; GI: gastrointestinal; HAE: hereditary angioedema; LTP: long-term prophylaxis; M: male.

at the European Academy of Allergy and Clinical Immunology (EAACI) Congress, July 2022.

OUTCOMES FROM THE NATIONAL UK SURVEY

The survey included 54 patients from 12 regional immunology centres within the UK who were treated with berotralstat.

The survey covered a 3-month period before commencing berotralstat, which was repeated at 3- and 6-month intervals following the commencement of berotralstat. The overall results revealed remarkable improvement in attack frequency following the commencement of berotralstat.[5] Data collated included previous prophylaxis, the prevalence of attacks, and quality of life scores via the Angioedema Control Test (AECT). The survey results were similar to the trial data; however, there was a higher percentage of patients discontinuing berotralstat because of adverse effects or unsatisfactory outcomes with regard to the efficacy of berotralstat than previously reported.[6]

OUTCOMES FROM SALFORD REGIONAL IMMUNOLOGY CENTRE

Ten patients were commenced on berotralstat since the launch of the EAMS in November 2020. Most of the patients (80%; n=8) either did not experience any adverse reactions or only mild symptoms that settled within a few days and continued their therapy. Only 20% of patients (n=2) reported unsatisfactory response to the drug and discontinued berotralstat. Regarding adverse reactions, 30% of patients (n=3) experienced mild headaches for a few days, and 20% (n=2) reported symptoms of gastrointestinal issues. Only one patient experienced cramps, nausea, diarrhoea, and vomiting, which settled within a few days.

In regard to previous use of long-term prophylaxis, 60% of patients (n=6) were established on oxandrolone as long-term prophylaxis treatment. Only 20% of patients (n=2) discontinued berotralstat because of an unsatisfactory response to prevent HAE attacks. These individuals restarted on oxandrolone. The rest of the patients (40%; n=2) successfully continued berotralstat and discontinued oxandrolone with no long-term adverse effects.

CONCLUSION

The authors' experience with berotralstat showed that most of the patients either did not experience any adverse effects or only mild symptoms that settled within a few days and continued berotralstat. Overall, there was a lower incidence of discontinuation because of adverse effects amongst the authors' cohort. More data from the post-marketing data is required to establish the real-world experience with regard to efficacy and adverse effects.

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Establishing New Standards in Hereditary Angioedema: Improving Outcomes Through Routine Prophylaxis

Interviewees:	Sorena Kiani Barts Health NHS Trust, London, UK
Disclosure:	Kiani has received research support and honoraria and/or consulting fees from BioCryst, Biotest, CSL Behring, KalVista, Pharvaris, and Shire/Takeda.

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Interview Summary

Hereditary angioedema (HAE) is a rare but debilitating and potentially fatal disease that presents in various forms, and can be difficult to manage. Its underlying cause is mutations in a gene that, through its protein product, controls production of the tissue enzyme kallikrein and a peptide mediator, bradykinin. The resulting overproduction of bradykinin leads to increased vascular permeability and oedema. Patients experience episodes of swelling that are unpredictable in their timing, location, and severity, and significantly affect quality of life (QoL), both physically and psychologically.

EMJ spoke to Sorena Kiani, Consultant Immunologist at the Barts Health NHS Trust (Barts), London, UK, who manages the UK's largest HAE patient cohort, ahead of a symposium held at the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress 2022 in Prague, Czechia. He explained how new specific medications to control and prevent HAE attacks, developed in the last decade, are giving clinicians and patients the opportunity to review treatment goals and raise expectations. Three prophylactic medications are now licenced for use and recommended in international treatment guidelines, which effectively prevent future HAE attacks.

Kiani describes clinical and real-world data from UK clinics that demonstrate how berotralstat, the first orally-administered HAE prophylaxis to be licenced, can reduce the number, duration, and severity of HAE attacks, resulting in measurable improvements in patients' QoL. He also discusses the importance of shared decision-making in developing individualised treatment plans that take into account patient goals and expectations. Kiani is confident that with wider access to prophylaxis, and appropriate monitoring and support, many more HAE patients can expect to live attack-free, with a normalised QoL.

INTRODUCTION

HAE is a genetic disorder affecting approximately 1:50,000 people worldwide, which causes unpredictable, recurrent episodes of cutaneous or submucosal oedema, affecting mainly the skin, abdomen, or upper respiratory tract. Laryngeal HAE attacks are a medical emergency and asphyxiation can occur, causing death in approximately 1 in 20 cases.[1]

A majority of cases of HAE are caused by mutations in the *SERPING1* gene that encodes the C1 esterase inhibitor (C1-INH) protein. The mutations result in an absence of C1-INH protein or abnormal functioning. Dysregulation of the bradykinin production pathway results, leading to increased vascular permeability and oedema.[2] Mutations have been found at multiple points in the C1-INH encoding gene, and the disease manifests as a spectrum with variations in the site, periodicity, and severity of disease in individual patients. Diagnosis is based on serum or plasma levels of C1-INH function, C1-INH protein, and complement factor 4.[3]

For many years, acute HAE attacks were treated with attenuated androgens. These anabolic steroids have also been used prophylactically to prevent further attacks. However, side effects with these agents are common and significant, including hirsutism, abnormal liver function, and thrombocytopenia.

In recent years, medications that specifically target the kinin–kallikrein pathway in HAE have been licenced, and have been shown to be effective in controlling and preventing attacks.[3] New international consensus guidelines[3] recommend three licenced medicines that provide effective prophylaxis to prevent HAE attacks. These are C1-INH protein, plasma-derived or recombinant, that replace the deficient C1-esterase inhibitor protein; lanadelumab; and berotralstat. Lanadelumab and berotralstat inhibit, by different mechanisms, the function of kallikrein, a protein involved in the bradykinin production pathway.[3]

Kiani spoke about the impacts of the updated treatment guidelines, his experiences of managing patients with HAE, and the benefits that new prophylactic approaches can bring to people living with HAE.

MANAGING HEREDITARY ANGIOEDEMA: FROM ACUTE THERAPY TO LONG TERM DISEASE CONTROL

Barts Health NHS Trust manages more than 200 patients with HAE, the largest cohort in the UK, including 40 paediatric cases. Kiani oversees an HAE family clinic at Barts, and explains: "Patients with HAE often experience their first attack during adolescence and, although many children have a parent with the condition, it is thought that up to 20% of patients present without a family history and have *de novo* mutations."

Kiani explained disease severity can vary from mild to severe disease, which can range from occasional to multiple attacks every week, making disease management challenging. "There is a wide spectrum of disease severity and also variation in the periodicity of attacks, which makes the condition very unpredictable. Some patients have relatives who have died of asphyxiation, and this can undoubtably cause intergenerational trauma in some cases. It is the unpredictability of the condition that can be so debilitating for patients who just want to be able to live a normal life," he says.

Currently, there is variation in patient access to treatments between and within countries, from a complete lack of access, to patients benefitting from on-demand medication that can be self-administered as soon as an HAE attack begins. On-demand medication is particularly important for patients who experience frequent attacks, if they are not already receiving prophylaxis. Guidelines recommend that patients carry sufficient medication to treat at least two attacks, to reduce the chance that they run out of on-demand medication.[3]

Early treatment of swelling episodes can help to reduce the severity and length of attacks.[4] However, as Kiani states: "If an attack is left untreated, there is an exponential rise in severity that means it becomes more difficult to treat." Other patients are at risk of attacks during surgical or dental trauma, where mechanical impact can trigger an attack to the upper airways. This risk can be mitigated by administration of short-term prophylactic medication, such as intravenous plasma-derived C1-INH.[3]

Kiani believes that more patients can benefit from access to prophylactic treatments to prevent HAE attacks. "Now there are three first line prophylactic therapies licenced, we are moving towards being able to prevent attacks, and more patients can expect to live a more normal life."

PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA

The 2021 International World Allergy Organization (WAO)/EAACI Guidelines[3] recommend use of one of three long-term prophylactic treatments to prevent future HAE attacks, which can be interchanged if response to one is poor. Long-term use of androgens is not recommended as first-line prophylaxis due to multiple potential side effects, including hirsutism and menstrual disorders in females, with multiple contraindications, including other medications such as statins and antidepressants.[5]

Two of the recommended prophylactic medications are injectable. Plasma-derived C1-INH, administered IV twice-weekly, has been shown to have good, dose-dependent effects in preventing HAE attacks.[6] Thromboembolic events are a rare side-effect, and the treatment is generally well tolerated but comes with the burden of injection. The alternative injectable is lanadelumab, a plasma kallikrein inhibiting monoclonal antibody that is typically administered once every two weeks, reducing to once a month for well-controlled HAE. Like C1-INH administration, in many instances, patients on lanadelumab can be trained to self-administer medication, reducing the need for visits to healthcare settings.

Berotralstat is the first oral prophylactic for HAE to be licenced and is a selective inhibitor of plasma kallikrein.[7] A randomised, double-blind, placebo-controlled Phase III trial (APeX 2) showed a 44% reduction in rate of HAE attacks compared with placebo ($p<0.001$) during the 24-week treatment period,[8] with improvements continuing up to 48 weeks.[9] At 96 weeks of treatment, patients who responded to the medication saw an average reduction of 80% from the mean baseline HAE attack rate per month. The study also showed that individuals switching to berotralstat monotherapy from injectable prophylaxis remained attack-free for more than 80% of the time.[10]

IMPROVING QUALITY OF LIFE FOR PEOPLE WITH HEREDITARY ANGIOEDEMA

Patients on long-term prophylaxis for HAE require regular monitoring, and the Angioedema Control Test (AECT) is a valuable standardised self-reporting scoring system, in which a score of nine or above indicates well-controlled disease.[11]

"If a particular prophylaxis is not controlling HAE attacks sufficiently, it is sensible to try an alternative," reiterates Kiani. In some cases where attenuated androgens are used, liver function may be normal, but the patient is anxious or unable to sleep. "In these cases, one may have to consider other prophylactic medications provided they fulfil the commissioning criteria." Before the introduction of berotralstat, in the UK at least, these patients would not be eligible for an alternative unless they went on to develop at least two HAE attacks per week (National Institute for Health and Care Excellence [NICE], unpublished data).

In Germany and several other European countries, access to berotralstat is unrestricted. In the UK, berotralstat is licenced for use in patients with HAE 12 years and older, and is now reimbursed on the National Health Service (NHS) for patients who have more than two HAE attacks per month (NICE, unpublished data). This means it is available for the majority of patients eligible for long-term prophylactic treatment.

In a survey of patients with HAE from 12 UK centres, including Barts, 54 patients with HAE receiving daily berotralstat (150 mg)[12] completed questionnaires, including AECT, to assess their experiences of taking berotralstat.[13] A mixed-effect model analysis of data from the 54 patients showed statistically significant reductions in the number of attacks for Months 1–3 of treatment (6.21±7.07 attacks) and Months 4–6 of treatment (4.54±5.49 attacks) compared with 3 months prior to treatment (12.91±7.94 attacks; n=28–33; $p<0.0001$). AECT scores improved significantly from the 3 months prior to treatment (AECT scores: 4.93±3.42) compared with AECT scores at 1–3 months (9.79±4.53 at 1–3 months and 11.03±3.14 at 4–6 months, respectively; n=32–43; $p<0.0001$). Twenty-two patients (40.7%) reported mild side effects, such as abdominal cramps.[13]

"Our real-world data from UK centres confirms that prophylaxis improves quality of life for most patients by reducing the number of HAE attacks and their

severity,"[13] confirms Kiani, who emphasises the importance of ensuring management plans are discussed and agreed with patients to support their needs, preferences, and lifestyle.

ACCESS TO MEDICINES AND ONGOING PATIENT SUPPORT ARE KEY TO ACHIEVING QUALITY OF LIFE GOALS

"Shared decision-making between the patient and physician on appropriate prophylaxis is vital to ensure the best outcomes for individual patients with different preferences and quality of life goals," Kiani asserts. Although some patients may benefit from prophylaxis with drugs such as berotralstat, Kiani says: "In the UK, patients can only be prescribed berotralstat as long-term prophylaxis if they have two or more attacks per month." This is an arbitrary cut-off and, he argues: "For some patients, one attack a month can be awful; you can end up being intubated in hospital, and off work for a week or more as a result of a single attack." These patients could benefit from prophylaxis. Kiani continues: "From a health economics perspective, huge savings could be made if clinicians were allowed to prescribe prophylaxis on a case-by-case basis, without restriction." Kiani referred to prescribing guidelines in Germany to highlight the benefits. "In Germany, all prophylactic agents are available without restriction, and this gives every patient with HAE the option to receive specific prophylactic treatment if it is clinically recommended."

From Kiani's experience, it is also clear that for patients to achieve an 'attack-free' norm, healthcare systems must provide regular patient monitoring, reviews and offer psychological support to patients. "At Barts, we offer a helpline with a dedicated member of staff and we aim to respond to every enquiry within 24 hours. We have three specialist nurses who are familiar with HAE, and can talk to patients and reassure them."

CONCLUSION

The availability of licenced long-term prophylactic treatments to prevent HAE attacks is changing the way HAE is treated, and is giving more patients hope for a future free from debilitating HAE attacks. Kiani believes more can be done to ensure every patient who could benefit has access to the prophylaxis that will help them reach this goal. He also urges providers to consider how they can improve their services to ensure patients feel supported and adhere to their prophylactic medication, and quality of life is normalised for as many patients with HAE as possible.

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EMJ Interview

Pavel Tolar

Division of Infection and Immunity, Institute of Immunity and Transplantation, University College London, UK

Pavel Tolar spoke with EMJ about his path to immunology, role in education, and fantastic achievements in his career.

Q1 What led you to embark upon a career in immunology and specifically in researching B cells?

When I studied medicine in Prague, I became interested in how cells make decisions to regulate various functions of the body. I thought immune cells were particularly interesting because they respond to unpredictable threats. I wanted to study lymphocytes but got a place in the lab of Peter Draber who was researching mast cells. This was my first exposure to the field of allergy, and I carried out my PhD there. Then, I joined a B cell lab headed by Susan Pierce at the National Institutes of Health (NIH) in the USA. The work on B cells was even more captivating, and we soon started making fascinating observations using imaging of live B cells, which was new at that time.

Q2 What would you say has been your most important discovery to date during your research on B cells?

When I founded my own lab back in Europe, at the National Institute for Medical Research and later at the Francis Crick Institute in London, UK, we discovered that B cells are very good at ripping foreign antigens from immune cells that collected and displayed these antigens on their surfaces for B cells to see. The mechanical vigour of the B cells intrigued us, and we described that the mechanical forces with which B cells pull on things actually help them to determine the quality of the binding of their B cell receptors to the foreign matter. This is similar to testing how sticky a surface is by touching it with a finger. Similarly to a very sticky surface, a strong B cell receptor binding promotes a stronger mechanical response and allows the B cells to extract more of the antigen. This helps B cells with better B cell receptors to dominate the immune response, and the system produces the highest quality antibodies.

More recently, we found that B cell activation works differently in B cells that express IgE. Their B cell receptors limit rather than promote their responses. For example, their B cell receptors curtail their lifetime once they become antibody-secreting cells, making IgE production transient. This natural regulation of IgE B cells may be broken in allergy. It seems that I circled back to studies of allergy after all.

Q3 In your research, you use myriad approaches, including immunology, genetics, biophysics, imaging, and nanotechnology. How

does this collaborative approach work on a logistical level and which is your favourite approach to use?

I have always been interested in using new and alternative approaches in biology. Biophysics, imaging, and computation are my favourites. However, it is challenging to pursue all of these approaches in one lab because it is not possible to recruit the best experts for each of these areas. Maybe the better route is for several labs to collaborate. Still, we do need to have an open mind because not all labs from different disciplines understand each other. A successful interdisciplinary collaboration is a great achievement.

Q4 Which new advances in immunology are you most excited about?

I think that high-throughput approaches brought power of scale to immunology. In B cell immunology, they transformed how we think about antibody specificity as well as the decisions that individual B cell clones make to produce antibodies binding to different targets. It is an interesting challenge to deconvolve the large sets of data into a mechanistic understanding of how things work.

Q5 In 2013, you were awarded the European Molecular Biology Organization (EMBO) Young Investigator Award. Could you tell us a little about this honour and how it has impacted your career?

Winning the EMBO Young Investigator Award was my dream as a student. The award opens fantastic access to EMBO resources and to the EMBO research community. EMBO support their researchers with almost no bureaucratic burden, which just makes research so much more enjoyable.

> "I think that high-throughput approaches brought power of scale to immunology."

Q6 In 2021, you began to work at University College London (UCL), UK, as Professor of B Cell Immunology. How are you finding your role and how does it differ from heading your own lab?

I am now part of a relatively new immunology department at UCL called the Institute for Immunology and Transplantation, which is becoming the largest cluster of immunologists in London. As a bonus, it is also a group of very nice people. The research remains the same; however, I now also teach, and we have more student projects in the lab.

Q7 As an educator, where do you think your focus will lie in the coming years?

We have been incorporating more B cell immunology into the UCL immunology lectures. I am also helping to run an interactive module that helps students to read and interpret research papers. I think this is a very important skill as it involves the very essence of scientific and logical thinking. Everybody should be trained in this.

Q8 You have published widely on B cells, writing and collaborating on many papers. Do you believe that there is a current gap in the literature, and which specific topics should be given more attention?

I think we still do not understand the principles that drive major decisions by which B cells regulate antibody production (e.g., to proliferate, die, or differentiate into antibody-secreting cells). Without this knowledge, it is difficult to understand how different types of B cells and B cells with different specificities for antigen respond to vaccines and infections. It is also hard to predict how B cells become a vehicle of diseases, such as in autoimmunity, lymphoma, or allergy. Many of the genes underlying human B cell deficiencies and diseases remain unidentified. There is a huge amount of work to be done here.

Q9 How has COVID-19 impacted your working model and the way that you approach your research?

With the worst of the pandemic hopefully behind us, I think we are left looking back and learning some lessons from how we worked over the past couple of years compared with normal times. I like the idea of being more flexible in where you work and how you meet. It is good to be back to discussing ideas in person; however, working online opens new possibilities as well as reduces travel, and we all became much better at this.

The EfficAPSI study

Real world effectiveness of Sublingual Allergen Immunotherapy on the onset and worsening of allergic asthma

Supported by an institutional grant

STALLERGENES GREER

Life *beyond* allergy

Overview

Study type

Retrospective pharmaco-epidemiological longitudinal study 'exposed/unexposed'

Study objectives

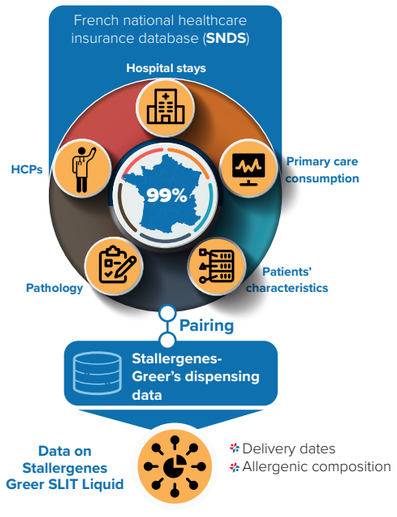
Assess the real-life impact of sublingual liquid allergen immunotherapy on:

- **PRIMARY** The onset and worsening of asthma in patients with allergic rhinitis (AR)
- **SECONDARY** Healthcare resources consumption in patients with AR

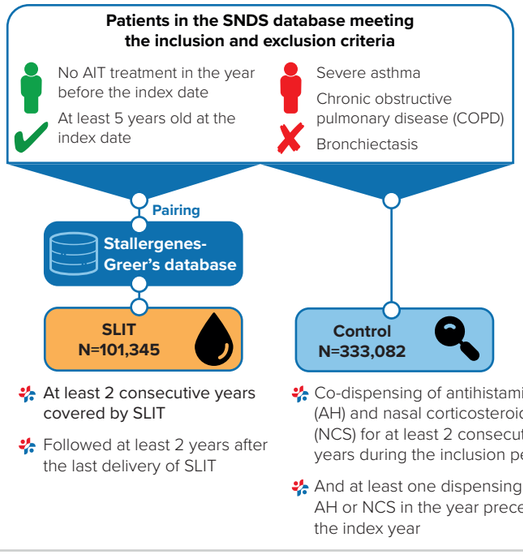
Scientific Committee

P. Devillier
P. Demoly
M. Molimard
JF. Bergman
B. Delaisi

Methodology



Study Population



Inclusion period:
2010–2013

Study period:
2010–2018

Index date:
SLIT:
First dispensing of SLIT
Controls:
First co-dispensing AH+NCS

Modelling and Analysis

Incidence of occurrence of an event of interest:

- The **hazard ratio** (HR) and **confidence interval** (CI) were estimated using a Cox proportional hazards model with inverse probability weighting (propensity score matching)
- The results were stratified according to: **the history of asthma** (yes/no), **age**, **allergenic composition**

Primary analysis

SLIT versus controls
(all patients without stratification)

Subgroup analysis

SLIT patients **WITH** asthma

SLIT patients **WITHOUT** asthma

Results

Primary analysis

SLIT versus controls

Association between SLIT* liquid and onset or worsening of asthma

Main definition (*more sensitive*):
New LTD (long term disease) for severe asthma OR hospitalization for asthma OR at least one dispensing of asthma treatment

Group	Number of patients	Persons years	Number of events	Raw incidence rate (%)
Controls	333,082	1,262,759	219,044	17
SLIT	101,345	403,427	56,365	14

Adjusted HR	95% CI
Ref	N/A
0.78	[0.77-0.78]

-22%
reduction of asthma events for SLIT versus controls

Secondary definition (*more specific, focused on severe forms of asthma*):
New LTD for serious asthma OR hospitalization for asthma

Group	Number of patients	Persons years	Number of events	Raw incidence rate (%)
Controls	333,082	2,537,074	11,775	0.46
SLIT	101,345	690,740	1,838	0.27

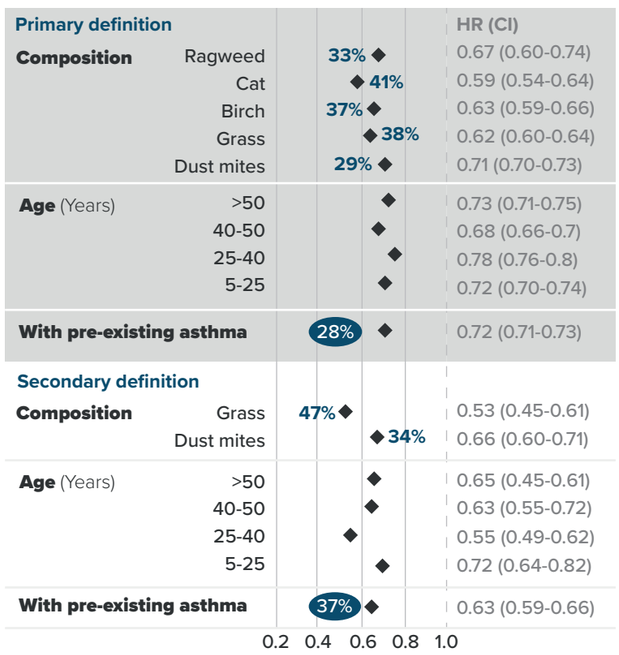
Adjusted HR	95% CI
Ref	N/A
0.72	[0.69-0.76]

-28%
reduction of asthma events for SLIT versus controls

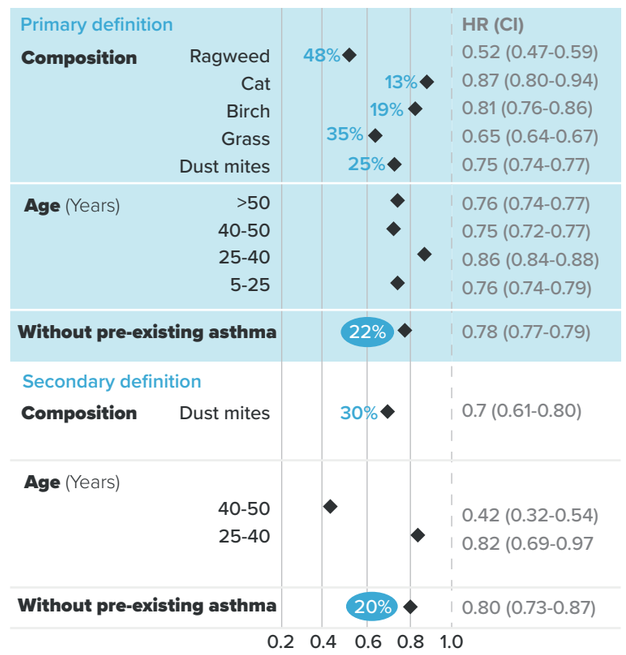
Subgroup analysis

SLIT versus controls

Patients **WITH** pre-existing asthma

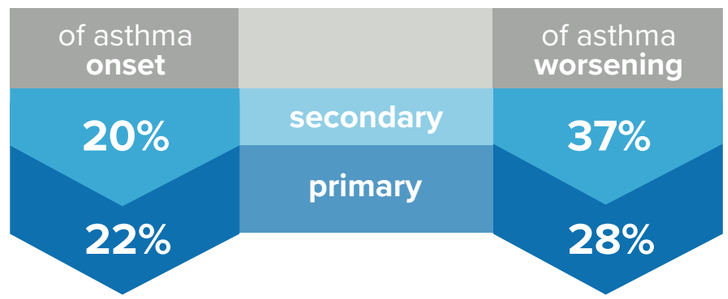


Patients **WITHOUT** pre-existing asthma



AIT is generally prescribed following or in association with symptomatic treatments

SLIT liquid is associated with a **significant reduction of the risk...**



In this nationwide, real-world study on a large number of patients, treatment with SLIT liquid* is effective in reducing the risk of asthma onset and worsening and has demonstrated its public health interest in real practice.

Paediatric Allergen-Specific Immunotherapy Studies Required by the European Medicines Agency: Is It Time for a Reassessment?

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Abstract

Allergen-specific immunotherapy (AIT) works well both in children and adults. An often-alleged gap between the level of evidence of AIT efficacy in adults versus children is based upon the flawed 'children-are-not-small-adults' and 'children-are-therapeutic-orphans' mantras, both of which emerged in the 1960s. These mantras led to paediatric legislation in the USA in 1997 and the European Union (EU) paediatric regulation 10 years later. Although preterm newborns and newborns are vulnerable, during the first year of life their organs mature. Young children are no longer physiologically newborns; their immune system can overreact and cause allergic reactions, and AIT works for them just like it does in adults. Young patients need dosing recommendations and safety observations, rather than repetition of proof of efficacy. Placebo-controlled efficacy studies withhold effective treatment, increase the risk of asthma in the placebo group and are, therefore, in the authors' opinion, unethical as well as in breach of the declaration of Helsinki. Individuals under the age of 18 years are not offered AIT treatments that are available to adults that are 18 years or older, but AIT treatment would be a suitable option. Since 2007, there were >100 EMA paediatric investigation plans that demanded 'paediatric' AIT studies involving tens of thousands of minors. Almost none were successfully undertaken and those that were done were unnecessary. It is time for the specialty of allergy to face this challenge.

INTRODUCTION

Allergology has struggled with the issue of whether children and adults are both successfully treated with allergen immunotherapy (AIT).[1] Some allergists emphasise the gap between the level of evidence of the efficacy of AIT in adults versus children.[2] The European Academy of Allergy and Clinical Immunology (EAACI) Future of the Allergists and Specific Immunotherapy (FASIT) working group published a consensus position in 2018. It criticised the European Medicines Agency (EMA) demands for 5-year double-blind placebo-controlled AIT efficacy trials in children that, in the placebo group, would prevent effective treatment and increase the risk of asthma.[3] However, it also attested to the European Union (EU) paediatric regulation that it enshrines the right for children to receive evidence-based medicine.[4] The EMA emphasises that children react differently to medicines and that, therefore, medicines need to be properly studied for safety and efficacy in minors.[5] Preterm newborns are indeed vulnerable and immature compared with adults. But minors mature physiologically well before their 18th birthday.[6,7] The reasons why many paediatric researchers are reluctant to apply the learnings of developmental pharmacology and physiology to the medical treatment of minors is based upon conflicts of interest that have slipped into the triangle of academic research, regulatory authorities, and the life science industry. In several large clinical areas, careers have been built on 'paediatric' studies, justified by the 'children-are-not-small-adults' and 'children-are-therapeutic-orphans'; mantras.[8-10] Allergology was not the core area where these mantras emerged. Rather, allergology was overrun by the wave of EMA-demanded paediatric studies from 2007.[11] Nevertheless, as long as this contradiction remains unaddressed in the world of allergology, it will persist.

HISTORY OF PEDIATRIC LEGISLATION IN THE USA AND EUROPEAN UNION

Labels describe the content of a product. After 1900, drug labels in the USA became more accurate regarding content and medical qualities.[12] However, labels are not instructions for physicians. Physicians can prescribe what they think will help their patient. Labels in the USA blocked trading of adulterated food and drugs. From 1962, manufacturers in the USA inserted paediatric warnings into drug labels to prevent damaging lawsuits in the litigious legal environment of the country, emphasising that no paediatric studies had been performed. These warnings were based on toxicities observed in preterm newborns treated in the 1950s with antibiotics, and on the U.S. Food and Drug Administration's (FDA) increased power with the new USA pharmaceutical legislation of 1962, reacting to the thalidomide catastrophe.[12] Since 1962, USA law requires proof of efficacy and safety of drugs before approval. Today, this principle is recognised worldwide.[13] Interpreting the paediatric warnings, the first chairman of the American Academy of Pediatrics (AAP) committee on drugs characterised children as "therapeutic orphans."[14] Furthermore, the AAP desired funds for paediatric research.

The term 'off-label' emerged in 1988.[15] The FDA prosecutes companies that encourage off-label use and discourages discussion of off-label use.[12] In 1977, the AAP complained that many drugs were not allowed to be advertised for children. In 1979, the FDA defined 'children' as <17-year-old. Since 1997, the USA rewards paediatric studies; since 2003, the FDA can mandate paediatric studies also without rewards.[8-10,16] The authors have used inverted commas because adolescents, for which the FDA requests many 'paediatric' studies, are physiologically no longer children, and school-age children 5–11 years of age are no longer newborns.

The EU paediatric regulation has been in effect since 2007. Also, EU researchers had desired more paediatric research. The EU regulation is currently more demanding than the regulation in the USA. For new drugs, companies must negotiate 'paediatric investigation plans' (PIP) with the EMA, committing to paediatric studies in persons <18-year-old. In contrast to the USA, paediatric studies are also demanded for rare diseases, vaccines, and biologics.

Table 1: Completed sublingual immunotherapy allergen-specific immunotherapy paediatric studies.

Product	NCT	Sponsor	Age	Number of patients	Start and end dates (years)	Comments
Grazax	NCT00408616[25]	ALK-Abelló (Hørsholm, Denmark)	5–16	253	2006–2007	Bufe A et al. (2009)[26]
Grass pollen	NCT00841256[27]	Allergopharma (Dermapharm, Grünwald Germany)	4–12	207	2008–2015	Wahn U et al. (2012)[28]
Grass pollen	NCT00550550[29]	MSD (London, UK)	5–17	345	2007–2009	Blaiss M et al. (2011)[30]
HDM	NCT01678807[31]	ALK-Abelló	12–17	195	2012–2013	Maloney J et al. (2014)[32]
GAP study	NCT01061203[33]	ALK-Abelló	5–12	812	2010–2015	Valovirta E et al. (2018)[34]
Ragwitek	NCT02478398[35]	MSD	4–17	1.025	2015–2019	EMEA-001881-PIP01-15

The EMA PIP decisions can be retrieved on the internet by entering the PIP number into any search engine.

GAP: grazax asthma prevention; HDM: House dust mites; PIP: paediatric investigation plan.

Table 2: Paul-Ehrlich-Institut-approved allergen-specific immunotherapy products in December 2021.

Description	Number	Approval date (years)	Approvals (2018–2021)
Oral immunotherapy	1	2020	1
Tree pollen SCIT	36	1989–1997	0
Grass pollen SCIT	50	1976–2005	0
House dust mites SCIT	21	1990–2004	0
Insects venom SCIT	18	1980–1997	0
Tree pollen SLIT	14	2004–2021	10
Grass pollen SLIT	32	2008–2020	5
House dust mites SLIT	10	2015–2021	7

SCIT: subcutaneous Immunotherapy; SLIT: sublingual immunotherapy.

THE HISTORY OF ALLERGEN IMMUNOTHERAPY PRODUCTS

For a long time, AIT products had been classified as individual products that only needed a production licence. However, European attitudes towards AIT had been different. The Nordic countries developed a standardisation of AIT products. In England, UK, AIT almost disappeared after anaphylactic reactions led to patients' deaths. Germany became the largest European AIT market, and its Paul-Ehrlich-Institut (PEI) had the highest competence among European authorities. The major AIT producers had developed their own systems for standardisation. In 1989, the EU classified AIT products as drugs, subjecting them to drug approval.[17,18] Details remained under the authority of individual states and, for a while, things carried on as before. PEI and German clinicians disliked the multitude of products of different quality. Two paths ensued. Switzerland, which is not part of the EU, allowed the retrospective approval of AIT products with the exception of recombinant allergens.[19] In contrast, the central EU paediatric regulation and a German initiative resulted in a challenge that, even today, is not resolved.

In 2008, Germany introduced an ordinance requiring new registration of AIT products as drugs (Therapieallergene-Verordnung).[20] Without submitting a marketing authorisation application, AIT products lost marketability after 3 years. If an application was submitted, the PEI could extend the deadline for clinical data submission. AIT products were now confronted with the EMA crusade for paediatric studies. The EMA and PEI jointly developed a 'standard PIP', now in its fourth version.[21] It mandates: a dose finding study in adults; a 1-year dose-finding-study in children or a justification why data can be extrapolated from adults; and for one leading product a double-blind 5-year placebo-controlled efficacy paediatric study (3 years for treatment and 2 years for follow-up) from each manufacturer. The AIT PIPs either demand separate studies in 5–11 and 12–17-year-olds, or a study in 5–17-year-olds with separate cohorts. Fifty-eight such 5-year double-blind placebo-controlled studies were demanded on the basis of the PIPs issued in 2010, respectively.[22] Together the 2 × 58 studies would have required tens of thousands of patients.[23]

The FDA does not mandate separate paediatric trials for AIT products. Four sublingual AIT products are today FDA-approved as drugs: Grastek (timothy grass pollen [ALK-Abelló, Hørsholm, Denmark]) from ≥5 years of age on; Oralair (grass allergens of sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass [Stallergenes Greer, London, UK) from ≥10 years on; Odactra (house dust mites [ALK-Abelló]); and ragwiteck (short ragweed pollen [ALK-Abelló]) in patients aged 18–65. These approvals are based on the age of the patients in the respective pivotal studies.

Apart from some small AIT studies,[24] very few paediatric studies have been performed for AIT in the last 15 years. Table 1 lists the six large completed paediatric studies with sublingual immunotherapy (SLIT). One study in house dust mites in patients aged 5–17 years was terminated following a drug safety monitoring board decision (NCT01199133).[36] In addition, an Oralair safety observation study was performed on 307 5–9-year-olds (NCT02295969)[37] and a Phase I safety study of house dust mites in 37 12–17-year-old patients (NCT01919554;[38] Table 1).

One paediatric SLIT study is ongoing (NCT03654976).[39] It is PIP-demanded (EMEA-001258-PIP01-11-M03) and placebo-controlled. Sponsored by ALK-Abelló, it has recruited 600 patients aged 5–17 years-old with asthma caused by house dust; it is no longer recruiting. Several more studies investigate AIT in both young and adult patients.

An oral immunotherapy product against peanut allergy, Palforzia (Aimmune Therapeutics, Brisbane, California, USA), was investigated in patients aged 4–55 years.[30] However, efficacy was shown only in patients aged 4–17.[41] Another PIP-demanded study was performed only in minors.[42] Today, Palforzia is FDA/EMA-approved in patients aged 4–17 and those becoming 18 during therapy.

Table 2 lists the PEI-approved AIT products.[43] Not one single subcutaneous Immunotherapy (SCIT) product received PEI paediatric approval after 2005. Of the 14 tree pollen SLIT 14 products, itulazax is from ALK-Abelló, with seven more itulazax products from various other companies. Two AIT products (SUBLIVAC® Birch

and SUBLIVAC Trees (HAL Allergy Group, Leiden, the Netherlands) were approved in 2018. Four staloral products were PEI-approved in 2004 and 2005. Of the 32 grass pollen SLIT products available, 11 are grasax products from various companies; 20 oralair products from various companies, and ragwizax from ALK-Abelló. Of the 10 house dust mice SLIT products, 5 acarizax products are from various companies; Aitaro and Amitend from ALK-Abelló; and 3 Orylmyte products from Stallergenes Geer.

To this day, there is a long list of AIT products that may still be marketed in Germany. They are not approved as drugs, but their marketing is tolerated for now.[44] EU-wide there are many more AIT products that still have a national marketing permission.[45] The 'paediatric' negotiations between the companies that sell these products and the authorities are ongoing. These products are still tolerated because, after the introduction of the Therapieallergene-Verordnung ordinance, the companies applied for an approval as drugs.[9-11]

DISCUSSION

There is a discrepancy between the multitude of EMA-demanded 'paediatric' AIT studies, the few initiated studies, and the fact that not one single SCIT product has been licensed in the allegedly paediatric population. Only SLIT studies were performed, initiated for products already FDA-approved as drugs.

Not all children are at risk from more toxicities, as claimed in the preamble of the EU paediatric regulation.[4] Clinical reviews list for AIT a lower age limit of 5 years, based on pragmatic considerations, and a contraindication for <2 years.[46] Allergy reviews also reveal the trouble many authors are experiencing trying to manoeuvre between the official regulatory situation and medical common sense.[3] Some authors appear to focus only on technical and clinical questions without addressing the current regulatory conundrum.[1]

Newborns and preterm infants are vulnerable. Within the first year of life, the organs that are responsible for absorption, distribution, metabolism and excretion mature.[7] Neonatal toxicities are no longer threatening. All drugs are dangerous in wrong doses. In the authors' view, young patients need child-friendly formulations and correct doses, rather than a separate proof of efficacy.[8-10]

USA-rewarded paediatric studies predominantly examine the use of drugs for adults in minors, rather than the medical needs of children.[47] Five years of placebo treatment in an allergy study that denies effective treatment will allow the potential progression to asthma in the placebo group and result in harm to the patients enrolled in the control group. The only reasonable justification for placebo-controlled efficacy trials would be if an adolescent patient's body and their immune system would undergo a fundamental metamorphosis at their 18th birthday, which would make it necessary to re-assess the efficacy of AIT in adolescents. However, the 18th birthday is only an administrative age limit, which does not correspond to a physiological change of the body. The majority of clinicians feel strongly about using the evidence of clinical studies as opposed to empirical evidence, which was satirised in a paper that questioned the efficacy of parachutes; double-blind randomised placebo-controlled trials are not needed to prove the efficacy of parachutes.[48] Critical papers,[8] a critical review of PIP-demanded AIT studies,[11] and two textbooks have recently been published on this topic.[9-10] FDA- and EMA/PIP-demanded paediatric studies are performed worldwide. Many paediatric AIT studies are based upon the uncritical and blurred FDA/EMA classification of children, which contradicts physiology and common sense.[6-8] The EMA admits that there are not enough patients worldwide for PIP-demanded studies.[49] A paper by FDA authors revealed that 94.5% of all drug adolescent dose recommendations were identical to adults.[50] In the authors' view, adolescents are legally still minor, but already mature physiologically.

In several clinical areas, the FDA has relented from its demand for separate paediatric studies, including in those adolescents who need medications for malignancies and antiepileptic drugs.[9-10,51,52] In contradistinction, the EMA has extended its demand for paediatric studies into adult diseases that occasionally occur before the 18th birthday, including amyotrophic lateral sclerosis, hepatic carcinoma, kidney carcinoma, and more.[9-10,53]

Today, most AIT studies that are not triggered by PIPs recruit both adults and minors. Some large companies decided that the financial investment to perform paediatric studies is worthwhile (Table 1). Participation in such studies results in participation at international investigator meetings, conference presentations, and funding. The results are often published in high-ranking journals. These studies promote paediatric careers in the FDA, EMA, pharmaceutical industry, and clinical research organisations. Allergology was not a clinical area with key clinical representation involved in shaping USA and EU paediatric laws.[9-10]

The young child at the beginning of the allergy career is prone for plasticity of the immune response, an argument often emphasised in textbooks and articles on AIT, with particular focus on children. This fact is an additional argument against demanding placebo-controlled proof-of-efficacy studies in minor patients.

In 2011, the European Academy of Allergy and Clinical Immunology (EAACI) tried to find a consensus with the EMA,[54] but did not address the key challenge: the blur between legal and physiological characterising of children.[8-10] After this meeting, EMA employees published a paper that documents how 'close collaboration' represents compliance to the association.[22] An EMA position paper still claims that off-label use in children is always dangerous,[55] without mentioning the life-saving achievements of paediatric oncology, neonatology, and further paediatric sub-disciplines that emerged off-label before the term off-label even existed.[15]

The EU paediatric regulation enforces additional regulatory studies in children that are not physiologically defined, neither vis-à-vis drug treatment nor *vis-à-vis* AIT, but chronologically, as <18 years of age. There are indeed fundamental differences between the physiology of preterm newborns and adults. But babies do not remain as immature and vulnerable as preterm newborns until their 18th birthday. The adolescents body is mature well before the 18th birthday, resulting, for example, in identical dose recommendations for adolescents and adults that resulted from many paediatric studies in adolescents, as reported by FDA authors.[44] The main changes in children's bodies and metabolism occur during the first 2 years of life, an age range in which AIT is not carried out.[46] The FASIT review repeats flawed EMA assumptions. The medical sense of 5-year double-blind placebo-controlled studies is criticised, as are PIP-demanded AIT paediatric studies in general.[3] In the authors' opinion, the conclusion that stakeholders must further discuss this issue is not sufficient. As long as EMA statements are taken at face value and conflicts of interest are not addressed, this issue will not be resolved.

The FDA has for decades prevented thalidomide-like catastrophes in drug development. Nevertheless, the artificial separation of adults and children has triggered a new worldwide challenge in medical research. Separate AIT paediatric regulatory studies are not only medically unnecessary, but also deny effective therapy to the control group, thereby increasing the risk of asthma. Although the authors have focused on the consequences for AIT, this challenge touches drug development in all clinical areas.[8-10]

The EMA PIPs have not advanced AIT in young patients.

CONCLUSION

Paediatric allergy should distinguish medically reasonable from unreasonable regulatory studies. Statements that there are limited paediatric data could be considered flawed in the context of this paper. Institutional review boards or ethics committees should suspend these ongoing unnecessary studies. Eventually, USA and EU paediatric laws need to be changed. The representative organs of paediatric allergology should distance themselves from questionable and potentially harmful studies. Allergologists should recommend to their colleagues who consider participation in allegedly paediatric studies to weigh in the benefit and risks for the patients, themselves, and the reputation of paediatric allergology. As everywhere in medicine, doctors in paediatric allergology have to differentiate between scientific findings, the requirements of the regulatory authorities, and the propaganda of drug manufacturers. It is their responsibility both to underage patients and to their parents. The described challenge is not limited to allergology. It is a challenge at the

interface between medicine and drug approval in general. But, as the authors have shown above, the demand by the EU regulatory authorities for questionable studies in children in the field of AIT is an extreme example that paediatric allergology has not yet adequately addressed. It is both a challenge and an opportunity for paediatric allergology to demonstrate its vigilance and independence.

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JAK Inhibitors in Rheumatoid Arthritis

Editor's Pick

The emergence of disease-modifying therapies for the treatment of rheumatoid arthritis has shown promise. This chronic disease results in debilitating outcomes in patients, and a reduced quality of life as a result. This article presents key information, trial data, and mechanisms of action of JAK inhibitors, which are now considered a key option for the treatment of rheumatoid arthritis. The authors also explore relevant uncertainties regarding the long-term safety of the therapies.

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Abstract

JAK inhibitors (JAKi) are targeted, small-molecule, disease-modifying therapies that are the newest class of treatments to emerge for the management of rheumatoid arthritis (RA) and the first oral disease-modifying anti-rheumatic drugs (DMARD) to demonstrate comparable clinical efficacy to biological DMARDs (bDMARD). In the UK there are four JAKi licensed for the treatment of RA (baricitinib, tofacitinib, upadacitinib, and filgotinib) and recent years have seen an explosion in their use. Clinical trial evidence supports their efficacy in a range of RA cohorts including DMARD-naïve patients and those with treatment-refractory disease. JAKi are associated with increased risk for infection, particularly herpes zoster virus reactivation, cytopenias, and hyperlipidaemia. In older patients with cardiovascular risk factors, post-marketing data suggest increased risk for malignancy, venous thromboembolism (VTE), and major cardiovascular events (MACE) with JAKi. This review article discusses the mechanism of action of JAKi and the evidence for their efficacy and side effect profile.

Key Points

1. JAK inhibitors (JAKi) have gained an important role in the management of rheumatoid arthritis, and current clinical guidance recommends their use in patients who have shown an inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD).

2. Current evidence suggests that JAKi are at least as efficacious as the previous standard of care therapies and that they are effective in a range of patient subtypes, including those with difficult-to-treat disease.

3. JAKi pose an increased risk of infection and there is concern that they increase the risk of malignancy, venous thromboembolism, and major cardiovascular events in certain patient groups; further research is needed to characterise this.

INTRODUCTION

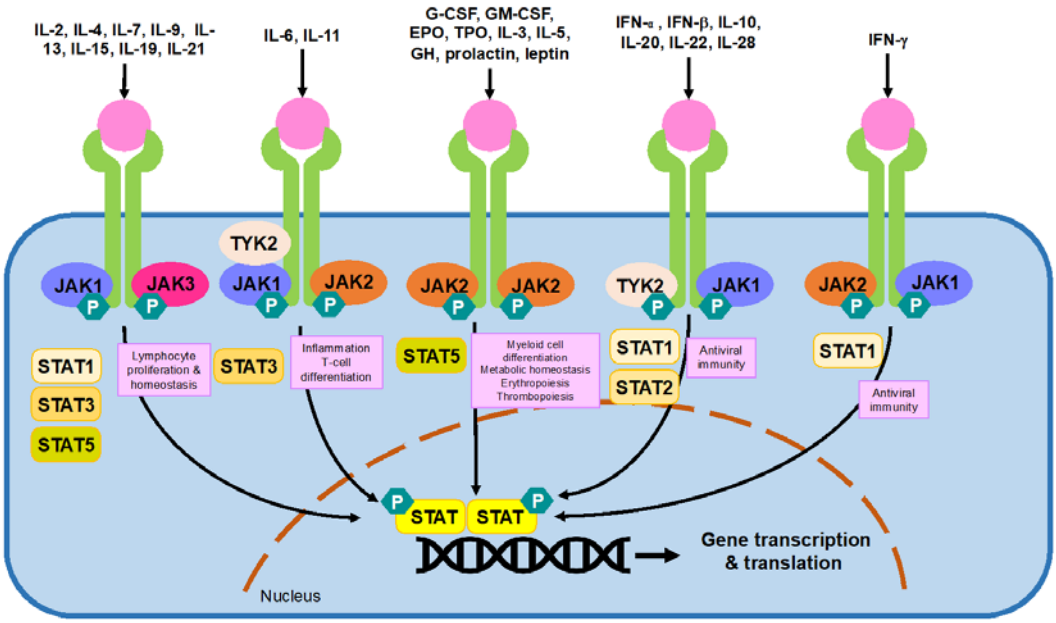
JAK inhibitors (JAKi) are the latest class of targeted, disease-modifying therapies licensed for the treatment of rheumatoid arthritis (RA). This review article discusses the role of JAKi in RA and their mechanism of action, before considering the evidence of their efficacy and adverse events.

RA is a chronic systemic inflammatory condition which, without early and effective treatment, results in progressive, erosive arthritis with pain, loss of physical function, joint deformity, and deterioration in quality of life.[1] Since the 1990s, the cornerstone of treatment has been conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD), with methotrexate commonly prescribed as first-line.[1] Many patients, however, may discontinue methotrexate therapy due to inadequate response (IR) to treatment, secondary loss of response, or the development of adverse effects (AE).[1,2] Beyond methotrexate, the past 20 years have seen the development and approval of more targeted treatments, including biologic DMARDs (bDMARDs) such as TNF inhibitors (TNFi); IL-6 and IL-1 inhibitors; anti-CD20 monoclonal antibodies; and cytotoxic T-lymphocyte antigen-4 inhibitors.[2] Despite these developments, only 40–50% of patients achieve disease remission.[2,3] Therefore, there remains an unmet need for RA management in terms of treatment tolerability and optimal disease control.[2,3]

JAK INHIBITORS AND THEIR MECHANISM OF ACTION

The latest class of drugs used in the treatment of RA are the JAK inhibitors (JAKi). JAKi are selective, small-molecule oral DMARDs that inhibit cytokine signal transduction via the JAK-signal transducers and activators of transcription (STAT) pathway.[1] There are four main JAK isoforms (JAK1, JAK2, JAK3, and tyrosine kinase 2), to which each JAKi exerts variable molecular selectivity, as summarised in Table 1.[1,2] As illustrated in Figure 1, JAKs exist with their associated STAT proteins to exert signal transduction.[1] JAK-STAT signalling is initiated when cytokines bind their cognate receptors on the extracellular surface membrane. This induces a conformational change in the receptor and the recruitment and activation of associated JAKs by phosphorylation.[1,2] Activated JAKs thereon auto-phosphorylate residues on the intracellular domains of the cytokine receptor, acting as docking sites for associated STAT proteins.[1] JAKs also phosphorylate STATs, which dissociate from their docking sites and dimerise to form phosphorylated STAT–STAT dimers. These translocate to the nucleus and bind to specific DNA regions, initiating gene transcription and hence protein translation.[1] Therefore, the net effect of the JAK-STAT signalling pathway is to stimulate gene expression in response to extracellular ligands. Different cytokines are dependent on different JAK and STAT proteins. This is summarised in Figure 1 and forms the theoretical basis for the development of isoform-specific inhibitors.

Figure 1: The JAK-STAT signal transduction pathway.



Adapted from Winthrop et al.[68] *and Harrington et al.*[1]

JAKs are activated when ligands, such as cytokines or growth factors, bind to their cognate receptor. JAK activation results in the recruitment, phosphorylation and dimerisation of STATs. STAT dimers translocate to the nucleus and stimulate gene transcription. As illustrated, different cytokine receptors preferentially use different JAK and STAT proteins to signal.

IL: interleukin, JAK: janus kinase, STAT: signal transducer and activator of transcription, TYK: tyrosine kinase, G-CSF: granulocyte colony-stimulating factor, GM-CSF: granulocyte-macrophage colony-stimulating factor, EPO: erythropoietin, TPO: thrombopoietin, GH: growth hormone, IFN: interferon, P: phosphorylation.

JAK INHIBITORS IN RHEUMATOID ARTHRITIS

In November 2012, tofacitinib became the first U.S. Food and Drug Administration (FDA)-approved JAKi for patients with moderate-to-severe RA with intolerance or IR to methotrexate.[4] Targeting the JAK pathway gained further pharmaceutical interest, resulting in the development of baricitinib in May 2018 and upadacitinib in August 2019.[1] In the UK, tofacitinib, baricitinib, and upadacitinib have all been recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of severe RA, and in February 2021 filgotinib became the first JAKi to become licensed for patients with moderate RA.[5] These recommendations have resulted in the widespread prescription of JAKi in the UK and worldwide. Throughout this review article, the authors review the latest data evaluating their efficacy and safety, focusing on tofacitinib, baricitinib, upadacitinib, and filgotinib.

EVIDENCE FOR THE EFFICACY OF JAKi IN RA

Clinical trial evidence strongly supports the efficacy of JAKi in the management of RA. In these studies, JAKi have been shown to significantly improve a range of RA-related outcomes, including disease activity, patient function, radiographic progression, and patient-reported outcome measures. Clinical efficacy has been demonstrated in a range of patient groups, including treatment of naïve patients and those with IR to csDMARDs and bDMARDs. Throughout the next section, the authors review the randomised controlled trial (RCT) evidence to support the use of the four JAKi licensed

Table 1: A summary of JAK inhibitors' selectivity, dosing, and current National Institute for Health and Care Excellence (NICE), U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA) approval status in RA.

JAKi	Manufacturer	JAK selectivity	Dose	Recommended by NICE for RA	FDA approval for RA	EMA approval for RA	Japan approval for RA
Tofacitinib	Pfizer (New York City, USA)	Pan-JAK	5 mg BD 11 mg OD	Yes: severe RA	November 2021	March 2017	March 2013
Baricitinib	Eli Lilly and Company (Indianapolis, Indiana, USA)	JAK1 and JAK2	2 mg OD 4 mg OD	Yes: severe RA	May 2018	February 2017	July 2017
Upadacitinib	AbbVie (Chicago, Illinois)	JAK1	15 mg OD	Yes: severe RA	August 2019	December 2019	January 2020
Filgotinib	Gilead Sciences, Inc. (Foster City, California, USA) and Galapagos Galapagos (Mechelen, Belgium)	JAK1	100 mg OD 200 mg OD	Yes: moderate RA	N/A	September 2020	September 2020
Peficitinib	Astellas Pharma Ltd. (Tokyo, Japan)	JAK3	25 mg OD 50 mg OD 100 mg OD 150 mg OD	N/A	N/A	N/A	March 2019

BD: twice daily; FDA: U.S. Food and Drug Administration; JAK: janus kinase; JAKi: janus kinase inhibitor; NICE: National Institute for Health and Care Excellence Clinical; OD: once daily; RA: rheumatoid arthritis; TEC: tyrosine kinase expressed in hepatocellular carcinoma.[1]

for the treatment of RA in the UK: tofacitinib, baricitinib, filgotinib, and upadacitinib. The major studies supporting their clinical effectiveness are outlined in Table 2.

Tofacitinib was the first JAKi to demonstrate clinical efficacy in the treatment of RA.[6] In the landmark ORAL Solo trial, tofacitinib demonstrated superiority over placebo in patients who were methotrexate-naïve with respect to American College of Rheumatology (ACR) response criteria, Health Assessment Questionnaire-Disability Index scores, and remission rates.[7] More recently, baricitinib, filgotinib, and upadacitinib have all demonstrated clinical efficacy in RCTs of participants with RA.[8-13]

Many effective treatments have been long-established in the management of RA. Therefore, head-to-head trials comparing JAKi to standard of care therapy were essential prior to clinical licensing. Current evidence suggests that JAKi are more effective than csDMARDs in some cases, with tofacitinib, baricitinib, and upadacitinib demonstrating superiority compared to methotrexate in RCTs.[14-17] In contrast, filgotinib did not produce superior ACR response rates compared to methotrexate in the FINCH3 RCT.[18]

Before the licensing of JAKi, bDMARDs were well-established as the gold standard treatment for RA, with their use preserved for patients with a IR to csDMARDs. As increasing evidence supporting the efficacy of JAKi emerged,

Table 2: Key randomised control trials providing evidence for the efficacy of JAK inhibitors in the treatment of rheumatoid arthritis in a range of patient subtypes.

Tofacitinib				Baricitinib			Filgotinib			Upadacitinib		
	RCT	BG therapy + trial arms	Endpoints	RCT	BG therapy + trial arms	Endpoints	RCT	BG therapy + trial arms	Endpoints	RCT	BG therapy + trial arms	Endpoints
MTX-naïve	ORAL -Start[14]	No BG 1. 5 mg BD 2. 10 mg BD 3. MTX	-ΔmTSS -ACR70	RA-Begin[15]	BG: None 1. 4 mg OD 2. 4 mg OD + MTX 3. MTX	-ACR20 -DAS28 (CRP) -HAQ-DI -MTSS -SDAI	FINCH -3[18]	No BG 1. 100 mg + MTX 2. 200 mg +MTX 3. 200 mg 4. MTX	-ACR20 -HAQ-DI -DAS28 (CRP) <2.6	SELECT -Early[17]	No BG 1. 15 mg OD 2. 30 mg OD 3. MTX	-ACR50 -DAS28 (CRP) <2.6
MTX-IR	ORAL -Scan[22]	BG MTX+ 1. 5 mg BD 2. 10 mg BD 3. PBO to tofacitinib at 6 months	-ACR20 -ΔmTSS -HAQ-DI -DAS28 (ESR) <2.6	RA- BEAM[8]	BG: MTX 1. 4 mg OD 2. ADA 3. PBO	-ACR20 -DAS28 (CRP) -HAQ-DI -mTSS -SDAI	FINCH -1[10]	BG: MTX 1. 100 mg 2. 200mg 3. ADA 4. PBO	-ACR20 -DAS28 (CRP) <3.2	SELECT -Monotherapy[23]	No BG 1. 15 mg OD 2. 30 mg OD 3. MTX to upadacitinib at Week 14	-ACR20 -DAS28 (CRP) <3.2
	ORAL -Standard[24]	BG MTX+ 1. 5 mg BD 2. 10 mg BD 3. ADA 4. PBO to tofacitinib at 6 months	-ACR20 -HAQ-DI -DAS28 -DAS28 (ESR) <2.6	RA-BALANCE[25]	BG: MTX 1. 4 mg OD 2. PBO to baricitinib at Week 24	-ACR20 -DAS28 (CRP) -CDAI<10 -SDAI<11 -HAQ-DI	DARWIN -1[69]	BG: MTX 1. 50 mg OD/BD 2. 100 mg OD/BD 3. 200 mg OD/BD 4. PBO	-ACR20 -DAS28 (CRP) -CDAI -HAQ-DI	SELECT -Compare[12]	BG: MTX 1. 15 mg OD 2. ADA 3. PBO	-ACR20 -DAS28<2.6 -Radiographic progression
	ORAL -Strategy[19]	No BG 1. 5 mg BD 2. 5 mg BD+MTX 3. ADA+MTX	-ACR50 -ACR20 -SDAI	RA-BEYOND[33] LTE study	BG: csDMARD 1.2 mg 2.4 mg	-CDAI <10	DARWIN -2[70]	No BG 1. 50 mg OD 2. 100 mg OD 3. 200 mg OD 4. PBO	-ACR20 -DAS28 (CRP) -CDAI -HAQ-DI			

Table 2 continued.

Tofacitinib				Baricitinib			Filgotinib			Upadacitinib		
	RCT	BG therapy + trial arms	Endpoints	RCT	BG therapy + trial arms	Endpoints	RCT	BG therapy + trial arms	Endpoints	RCT	BG therapy + trial arms	Endpoints
csDMARD -IR	ORAL -Solo[7]	No BG 1. 5 mg BD 2. 10 mg BD 3. PBO to tofacitinib at 3 months	-ACR20 -HAQ-DI -DAS28 (ESR) <2.6	RA-Build[9]	BG: csDMARD 1. 2 mg OD 2. 4 mg OD 3. PBO	-ACR20 -DAS28 -SDAI <3.3 -HAQ-DI	N/A	N/A	N/A	SELECT -Next[13]	BG: csDMARD 1. 15 mg OD 2. 30 mg OD 3. PBO	-ACR20 -DAS28 (CRP) <3.2
	ORAL-Sync[26]	BG csDMARD + 1. 5 mg BD 2. 10 mg BD 3. PBO to tofacitinib at 6 months	-ACR20 -HAQ-DI -DAS28 (ESR) <2.6									
bDMARD-IR	ORAL-Step[27]	BG MTX + 1. 5 mg BD 2. 10 mg BD 3. PBO to tofacitinib at 6 months	-ACR20 -HAQ-DI -DAS28	RA-Beacon[28]	BG: csDMARD 1. 2 mg OD 2. 4 mg OD 3. PBO	-ACR20 -HAQ-DI -DAS28 (CRP) -SDAI <3.3	FINCH -2[11]	BG csDMARD 1. 100 mg 2. 200 mg 3. PBO	-ACR20 -DAS28 (CRP) <2.6 -HAQ-DI	SELECT -Beyond[29]	BG: csDMARD 1. 15 mg OD 2. 30 mg OD 3. PBO to upadacitinib at 12 weeks	-ACR20 -DAS28 (CRP) <3.2
		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	SELECT -Choice[20]	BG: csDMARD 1. 15 mg OD 2. ABA	- DAS28 (CRP) - DAS28 (CRP) <2.6

BD: twice daily; FDA: U.S. Food and Drug Administration; JAK: janus kinase; JAKi: janus kinase inhibitor; NICE: National Institute for Health and Care Excellence Clinical; OD: once daily; RA: rheumatoid arthritis; TEC: tyrosine kinase expressed in hepatocellular carcinoma.[1]

the question as to whether they could be as efficacious as bDMARDs arose. This led to the planning and execution of four pivotal head-to-head RCTs, all of which suggested that JAKi were at least as efficacious as the TNFi adalimumab.[8,10,12,19] These trials included the ORAL-STRATEGY and FINCH-1 trials, which demonstrated non-inferiority of tofacitinib and filgotinib to adalimumab in the management of RA.[10,19] The RA-BEAM trial was a pivotal head-to-head study that compared baricitinib and adalimumab in participants with RA with IR-methotrexate.[8] In addition to demonstrating non-inferiority compared to adalimumab, baricitinib was superior with respect to ACR20 response rate and disease activity measured using the Disease Activity Score (DAS)-28.[8] RA-BEAM was the first RCT to demonstrate superiority of JAKi to biological medications, and led to the rapid uptake of these medications in clinical practice. More recently, upadacitinib has also demonstrated superiority compared to bDMARDs, including adalimumab and the cytotoxic T-lymphocyte antigen-4 inhibitor abatacept.[12,20] There have been no head-to-head trials comparing JAKi to other classes of biologics such as IL-6 or CD20 inhibitors.

DIFFICULT TO TREAT RHEUMATOID ARTHRITIS

The aforementioned evidence supports the clinical efficacy of JAKi in RA, and suggests that they are at least as efficacious as the current standard of care. Importantly, clinical trial data also demonstrates the effectiveness of JAKi in patients with refractory disease who have shown IR to csDMARDs and bDMARDs. This is an important group to consider, as a significant proportion of patients with RA do not respond to first- or second-line therapies.[21]

Table 2 summarises the RCTs investing the efficacy of JAKi in patients with RA who are methotrexate-naïve and those with IR-methotrexate, IR-csDMARDs, and IR-bDMARDs. Notably, there is an abundance of Phase III evidence supporting the efficacy of JAKi in patients with IR to csDMARDs and methotrexate.[7-10,12,13,19,22-26] Furthermore, tofacitinib, baricitinib, upadacitinib, and filgotinib have also demonstrated clinical efficacy in patients who have previously received at least one bDMARD.[11,27-29] Registry data from a Japanese cohort of patients with RA with difficult to treat disease, defined as previous IR to two or more bDMARDs or targeted synthetic DMARDs, found that JAKis were associated with the highest proportion of rapid responders and the best outcome in clinical disease activity index in comparison to other bDMARDs or targeted synthetic DMARDs.[30] Overall, these data suggest that JAKi can play important roles as second-, third-, or fourth- line therapies in patients who have failed previous treatments, and emerging data suggest that they may be preferable in this setting.

ADDITIONAL CONSIDERATIONS

JAKi In Combination or Alone?

Current guidelines support the administration of JAKi alongside csDMARD therapy. This is in accordance with RCT evidence suggesting that JAKi are more efficacious in combination than as monotherapy. For example, in the ORAL-STRATEGY trial, treatment with tofacitinib and methotrexate was associated with increased rates of ACR response, low disease activity, and clinical remission, compared to tofacitinib monotherapy.[19] Superior outcomes with combination therapy have also been demonstrated in trials of baricitinib and filgotinib.[15,18]

Initial Dosing of JAKi

Current clinical guidelines advise that JAKi doses may be adjusted with increased age, or with liver or renal impairment.[31] In the absence of these exceptions, patients are generally

commenced on standard doses of JAKi (summarised in Table 1). As illustrated in Table 2, RCTs have investigated the relative efficacy of different doses of JAKi. Some of these studies suggest that the higher of the licensed doses are associated with increased clinical efficacy; however, this should be balanced against the possibility of increased risk of adverse events, which will be discussed later.[10] In contrast, other data suggest no difference in efficacy between doses. For example, a meta-analysis showed no difference in clinical outcomes including the ACR20, DAS-28, and Health Assessment Questionnaire-Disability Index, between the licensed doses of baricitinib, tofacitinib, and upadacitinib.[32]

Tapering of Doses?

In patients with RA on long-term JAKi, clinical guidance suggests that the dose may be tapered when clinical remission is achieved.[31] The evidence for this is lacking, but has been investigated in patients on baricitinib in the RA-BEYOND trial. This trial studied patients with RA on baricitinib with low disease activity (LDA), or in remission.[33] In this trial, participants were randomised to continue at a 4 mg daily dose, or to reduce to 2 mg. This study demonstrated that dose reduction was associated with a small but significant fall in those sustaining LDA or remission. Whilst there was a higher risk of relapse in the group taking 2 mg baricitinib (37% versus 23%; p=0.001), most patients on the lower dose maintained LDA.[33] Furthermore, patients who were weaned to 2 mg could recapture remission if returned to 4 mg daily.[33] Therefore, these data suggest that most patients on long-term JAKi therapy maintain LDA when weaned to lower doses. If relapse occurs, LDA can usually be recaptured by increasing the dose.[33]

Predictors of Response to JAKi

As an increasing number of therapies are licensed for RA, predictors of treatment response have gained interest. Post-hoc analysis of five Phase III studies found that patients with RA with positivity for anti-cyclic citrullinated peptide and rheumatoid factor were more likely to achieve ACR 20/50/70 responses than seronegative patients.[34] DAS-28 remission rates and quality of life measures were also lower in anti-cyclic citrullinated peptide-negative patients.[34] There were no other significant differences between achievement of endpoints in seronegative versus seropositive patients.[34] Future work is needed to confirm this finding and to explore other markers of treatment response.

Comparative Efficacy of JAKi

The relative efficacy and safety of different JAKi is an area of uncertainty, and there have been no head-to-head comparison studies in this area. Indirect comparison using meta-analyses of RCT data have attempted to characterise the differences between JAKi. Due to study heterogeneity, these indirect analyses must be interpreted with caution, and conclusions can be misleading.

Lee et al.[31] performed a network meta-analysis to evaluate the comparative efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib, and perficitinib as monotherapy in individuals with RA. Five RCTs with a total of 1,547 patients were included in the analysis.[31] The analysis found that all five JAKi were associated with a significantly higher ACR20 response rate than placebo. Peficitinib 150 mg was found to be the most efficacious JAKi, measured using the probability of achieving the ACR20.[31] Peficitinib 150 mg was followed by pefictinib 100 mg, filgotinib 200 mg, filgotinib 100 mg, tofacitinib 5 mg, upadacitinib 12 mg, and baricitinib 4 mg in achieving ACR20. ACR50 and 70 response rates showed similar patterns.[31]

In contrast with the results from Lee et al.,[31] two meta-analyses have suggested that upadacitinib is the most efficacious JAKi.[32,35] Pope et al.[35] reported that upadacitinib was more effective when compared to tofacitinib and baricitinib. Furthermore, Weng et al.[32] found that upadacitinib was the most efficacious JAKi in a meta-analysis comparing the relative efficacy of csDMARDs, bDMARDs, and JAKi in patients with RA with IR to at least one csDMARD.[32] In this study, 88 studies and 31,566 patients were included. bDMARDs and JAKi were more efficacious than placebo in all three measures of drug efficacy.[32] Whilst upadacitinib was the most efficacious JAKi, the IL-6 inhibitor tocilizumab was the most efficacious medication in improving DAS-28 scores.[32]

Real-world studies have also investigated the relative efficacy of JAKi by analysing registry data. In one such study, baricitinib was shown to demonstrate significantly better clinical outcomes, measured using clinical disease activity index, and similar safety profiles when compared to tofacitinib.[36] These data should be interpreted with caution due to a small sample size (n=294).[36]

In summary, there is an abundance of evidence supporting the clinical efficacy of JAKi in the treatment of RA. Current evidence suggests that JAKi are at least as efficacious as the previous standard of care therapies and that they are effective in a range of patient subtypes, including those with difficult-to-treat disease. Trial evidence supports a beneficial effect of combination therapy, with guidance suggesting that JAKi should be prescribed alongside csDMARDs. The major outstanding area of uncertainties relate to the comparative efficacy between individual JAKi, and between JAKi and bDMARDs.

SIDE EFFECTS AND SAFETY PROFILE

JAKi have been associated with a broad range of side effects, summarised in Table 3. Most notably, increased risk of infection, malignancy, venous thromboembolism (VTE), and major cardiovascular events (MACE) have been described in patients receiving JAKi. The evidence for this will be summarised in the next section of the review.

Infection

In similarity to other immunomodulatory therapies, the most commonly reported AEs with JAKi are infections.[37] The risk of infection with JAKi has been evaluated in Phase II, Phase III, and long-term extension (LTE) studies, with incident rate (InR) estimates ranging between 1.6 and 3.0 per 100 patient-years (PY) for those on JAKi.[38-41] In these studies, the rates of serious infection are stable over time with pneumonia being the most commonly reported.[42] In studies of JAKi, risk factors for infection include age, steroid usage (prednisolone ≥7.5 mg/day), disease activity, diabetes, and higher dosage (10 mg twice daily [BD] versus 5 mg BD).[42-44] Similar rates of infection have been reported in patients receiving baricitinib, upadacitinib, and filgotinib, with meta-analyses demonstrating no significant difference in infection risk between JAKi.[40,41,45,46]

The relative risk for infection in patients taking JAKi seems comparable to those taking bDMARDs, with one retrospective cohort study reporting no significantly increased risk of serious infection with tofacitinib compared with TNFi.[47] Similar rates of infection in participants taking JAKi and bDMARDs have also been demonstrated in head-to-head RCTs and in post-approval registries.[8,10,12,24,48] In elderly patients, the German prospective register RABBIT reported that csDMARDs, bDMARDs, and JAKis were associated with similar rates of infection.[44] Whether there are differences in the pattern of bacterial infection between JAKi and bDMARDs remains an area of uncertainty.[49]

Herpes Zoster

The reactivation of herpes zoster virus (HZV) is a widely recognised complication of JAKi, with trial data showing a greater risk of HZV with JAKi compared to placebo, csDMARDs, and bDMARDs.[49] In Phase II, Phase III, and LTE studies, the IR of HZV ranges between 1.1 and 3.6 per 100 PY for those on JAKi.[38-41] Rates of HZV are higher in Asian countries, including Japan (IR=8.0 per 100 PY) and Korea (IR=8.4 per 100 PY); however, the reasons for this are unclear.[38] In studies of tofacitinib, significant risk factors for HZV include age, corticosteroid use, co-prescription of methotrexate, smoking, and higher JAKi dose.[38]

As summarised in Table 3, the rates of HZV reactivation appear similar between tofacitinib, baricitinib, and upadacitinib.[39-41] Pooled data evaluating JAK1 selectivity suggest that filgotinib is associated with fewer HZV infections; however, further data are required to conclude this.[49] In comparison with bDMARDs, HZV is seen significantly more frequently with JAKi. In one study, the crude IR for HZV in patients with RA receiving tofacitinib was 3.87 per 100 PY (95% confidence interval [CI]: 2.92–5.32), compared with 1.95 per 100 PY in patients on adalimumab (95% CI: 1.65–2.31).[50] This has also been reported in post-approval registry studies, including the American CorEvitas register, where the hazard ratio for HZ

Table 3: A summary of the common adverse events from four long-term integrated safety analyses of four JAK inhibitors in the treatment of rheumatoid arthritis. Other safety concerns are summarised in the lower half of the table.

	JAK inhibitors and doses				
	Tofacitinib[62]	Baricitinib[39]	Upadacitinib[46]	Filgotinib[41]	
Number of patients (n)	7,061	3,770	651	3,691	
Total exposure (patient years)	22,875	14,774	2,796	6,080	
Adverse effects IR (95% CI)	Doses				
	All doses (5 mg–10 mg BD)	All doses (2–4 mg OD)	15 mg OD	100 mg OD	200 mg OD
Serious infection	1.5 (2.4–2.7)	2.6 (2.33–2.86)	3.0 (2.4–3.7)	3.1 (2.1–4.5)	1.6 (1.2–2.1)
HZV	3.6 (3.4–3.9)	3.0 (2.70–3.28)	3.1 (2.5–3.8)	1.1 (0.8–1.7)	1.8 (1.4–2.3)
Opportunistic infection	0.4 (0.3–0.5)	0.5	0.4 (0.2–0.7)	0.2 (0.1–0.5)	0.1 (0.1–0.3)
TB	0.2 (0.1–0.2)	0.1 (0.08–0.20)	0.1	0.1 (0.0–0.5)	0.0
Malignancy (excluding NMSC)	0.8 (0.7–0.9)	0.6 (0.34–0.91)	0.6 (0.4–1.0)	0.5 (0.3–1.0)	0.6 (0.4–0.9)
NMSC	0.6 (0.5–0.7)	0.3 (0.25–0.44)	0.3 (0.1–0.5)	0.1 (0.0–0.5)	0.6 (0.4–0.9)
Lymphoma	0.05 (0.03–0.09)	0.06 (0.03–0.11)	N/A	N/A	
VTE	0.3 (0.2–0.3)	0.49 (0.39–0.61)	0.3 (0.1–0.6)	0.0 (0.0–0.3)	0.2 (0.1–0.4)
DVT	0.2 (0.1–0.2)	0.35 (0.26–0.45)	N/A	0.0	0.1 (0.1–0.3)
PE	0.1 (0.1–0.2)	0.26 (0.18–0.35)	N/A	0.0 (0.0–0.3)	0.1 (0.1–0.3)
MACE	0.4 (0.3–0.5)	0.5 (0.40–0.64)	0.4 (0.2–0.7)	0.6 (0.4–1.1)	0.4 (0.2–0.7)
Other safety concerns[71]					
	Haematological abnormalities: anaemia, cytopenia				
	Biochemical abnormalities: increased lipids, increased AST/ALT, increased CK				
	Gastrointestinal perforation				
	N/A	N/A	N/A	Male infertility	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BD: twice daily; CI: confidence interval; CK: creatine kinase; DVT: deep vein thrombosis; HZV: herpes zoster virus; InR: incidence rate: MACE: major adverse cardiovascular event; N/A: not applicable; NMSC: non-melanoma skin cancer; OD: once daily; PE: pulmonary embolus; TB: tuberculosis; VTE: venous thromboembolism.

reactivation was 2.32 (95% CI: 1.43–3.75) for tofacitinib versus bDMARDs.[48]

Malignancy

The overall risk of malignancy in patients with RA is moderately elevated when compared to the general population.[51] There is concern that JAKi increase this risk further by preventing the immune-mediated elimination of cancerous cells through decreased interferon production and reduced circulating natural killer cells.[37,52] Pooled data from Phase II, Phase III, and LTE studies found 107 of 5,671 patients with RA treated with tofacitinib developed malignancies (excluding non-melanoma skin cancers) with the commonest being lung (n=24), breast (n=19), lymphoma (n=10), and gastric cancer (n=6).[53] The rate of malignancy was stable at 6-month intervals and comparable to that seen in the general RA population.[53] Similar rates have been reported with baricitinib, upadacitinib, and filgotinib.[39-41] In similarity to bDMARDs, the risk of non-melanoma skin cancers may be raised with JAKi; however, the evidence is not clear.[54]

A systematic review and meta-analysis of RCTs and LTEs concluded that tofacitinib showed no significantly increased risk of malignancy in patients when compared with those receiving csDMARDs or placebo.[55] In contrast, the ORAL Surveillance post-authorisation trial found that tofacitinib was associated with increased risk of cancer, when compared with a TNFi, in a cohort of older patients.[56] It is unclear whether the risk of malignancy was increased with JAKi or decreased with TNFi. Nevertheless, the FDA issued a warning for the use of tofacitinib and JAKi in the elderly population, and TNFi may be preferable in this cohort, pending further clarity.[53,61,62]

Thromboembolic Events

Immune-mediated inflammation, as occurs in RA, is a risk factor for VTE (including pulmonary embolism and deep venous thrombosis). A nationwide register-based cohort study found that patients with RA were 1.88 times more likely to develop VTE than those without.[57] In this study, disease activity was a significant risk factor for VTE, with a two-fold increase in risk in patients with disease remission compared to high disease activity.[57]

There has been concern that JAKi are independent risk factors for VTE, with some trial and post-marketing evidence suggesting increased risk with baricitinib and tofactinib.[58] Although the interpretation of these data is limited by small event numbers, the labelling for tofacitinib, baricitinib, upadacitinib, and filgotinib list thrombosis as a warning and clinicians are advised to use with caution in those with underlying risk factors.[59-61] In Phase II, Phase III, and LTE studies of patients with RA receiving JAKi, IR estimates for VTE range between 0.17 and 0.49 per 100 PY, with rates stable over time, similar between JAKi subclasses, and higher in those with background thrombotic and cardiovascular risk factors.[39-41,60,62] Long-term safety data for tofacitinib suggest that the risk for VTE is dose-dependent, with increased rates in those taking 10 mg BD, a dose that is licensed for ulcerative colitis and not RA.[43] This was also demonstrated in the ORAL surveillance study, where a higher risk for VTE was seen with tofacitinib 10 mg BD versus TNFi, but not with 5 mg BD.[56]

In contrast to current warnings, a meta-analysis of 42 RCTs found no increased risk for VTE in those receiving JAKi compared to placebo.[61] Furthermore, real-world evidence using registry data from >85,000 patients with RA receiving JAKi or TNFi showed no evidence for increased risk for VTE with tofacitinib.[57] These results are reassuring but should be interpreted with caution in patients with underlying risk factors for VTE, in whom JAKi are generally avoided.[61]

Major Adverse Cardiovascular Events

Patients with RA have an approximately 70% higher risk of cardiovascular (CV) disease compared to the general population.[63] Safety data are generally reassuring and suggest that the observed MACE IR ranges between 0.4 and 0.6 per 100 PY in those treated with JAKi, which is comparable to the general RA population.[41,46,64] In contrast, the ORAL Surveillance study found that the incidence of MACE were higher with tofacitinib compared to TNFi (hazard ratio: 1.33; 95% CI: 0.91–1.94).[56] In older patients with at least one CV risk factor, tofacitinib was associated with more MACE compared to TNFi.[56,65,66] These results were extrapolated to all JAKi, and in September 2021

the FDA released an updated black box warning regarding increased risk of death, CV disease, malignancies, and thrombosis in those on JAKi versus TNFi.[56,65,66] As TNFi are known to decrease the risk of MACE in RA cohorts, the results from the ORAL surveillance study could suggest that TNFi are relatively more protective against MACE than JAKi.[34] Whilst further work sheds insight in this area, TNFi may be preferable to JAKi in patients with RA with pre-existing CV risk factors.

SUMMARY

JAKi have gained an important role in the management of RA, and current clinical guidance recommends their use in patients who have shown a IR to csDMARDs. RCTs to date support the efficacy of JAKi in a range of patient groups, but there remain outstanding areas of uncertainty. Most notably, the comparative efficacy and safety of the different JAKi remains unclear, and meta-analyses in this area have produced conflicting results. Although the different JAKi exert differential isoform selectivity, differences between JAKi in efficacy or AEs have not been observed in trial or real-world data. Furthermore, whilst head-to-head trials have compared the efficacy of JAKi to TNFi, there have been no head-to-head studies characterising the relative efficacy of JAKi compared to bDMARDs such as IL-6 inhibitors. In those who have received JAKi, there is uncertainty as to whether switching between JAKi is effective following IR to primary JAKi. Overall, further work is needed to characterise the predictors of response to JAKi, in addition to csDMARDs and bDMARDs, with personalised medicine being the ultimate aim in the treatment of RA.

In addition to uncertainties regarding efficacy, the long-term safety of JAKi is relatively unclear, and there are ongoing safety concerns. Most notably, tofacitinib has been associated with increased cardiovascular disease and cancer, in comparison to TNFi, in older adults.[56] Other areas of uncertainty include the risk of testicular toxicity with filgotinib,[67] the risk of VTE in patients with thrombotic risk factors, and the relative safety of the different JAKi. Future work is needed to address these issues and confirm which patient groups can be given JAKi without significant risk of adverse outcomes.

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Central Role of Mast Cells in Mastocytosis, Hereditary α-Tryptasemia, Mast Cell Activation Syndrome, Urticaria, and Angioedema

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Abstract

Mast cells are the central cells in the pathogenesis of many conditions that are associated with mediator release. New information is emerging about the role of mast cells in a number of conditions. This review summarises current knowledge on the topic.

Some conditions such as mastocytosis have a confirmed genetic background; however, the genetic background of hereditary α-tryptasemia has only recently been described, and routine testing is yet to be set up in genetic laboratories. It is still unknown whether there is a genetic predisposition leading to the development of mast cell activation syndrome as well as urticaria and angioedema, and research is under way in this direction.

The best known mediator contained in mast cells is histamine 2-(4-imidazolyl)-ethylamine, but it is not the only one. The effects of other mediators are significant in mast cell-mediated conditions, and can be future therapeutic targets. Diamine oxidase deficiency is responsible for digestive issues in some people, and although not directly linked with mast cell pathology, it falls under this umbrella due to symptoms related to the effects of externally consumed histamine.

Mast cell-mediated diseases are usually defined through the detection of an elevation of mast cell mediators, response to antihistamines, mast cell stabilisers, and, in some cases, anti-IgE treatment when indicated. They comprise of mastocytosis, hereditary α-tryptasemia, mast cell activation syndrome, urticaria, and angioedema.

Key Points

1. The understanding of the role of mast cells in different conditions is evolving, which may contribute to an improved patient quality of life.

2. Mast cell activation syndromes are prevalent and heterogeneous, with an unclear aetiology at present.

3. Mast cells are essential in several antiparasitic responses, although they can also contribute to hypersensitivity reactions.

INTRODUCTION

Mast cells are at the centre of many conditions, leading to symptoms associated with mediator release,[1-6] and have been implicated in many diseases beyond allergy.[7] Mastocytosis-associated hereditary tryptasemia has a defined genetic background. Other mast cell related conditions are deemed to have external activation of the mast cells through the mechanisms of auto allergy and autoimmunity.[8]

The quality of life (QoL) of patients with a range of mast cell mediated diseases is significantly compromised, and the evaluation of QoL is not regularly performed in clinics. However, it is very important to assess the patients' QoL in light of a steady increase in the prevalence of mastocytosis, chronic spontaneous urticaria (CSU) and angioedema, atopic and contact dermatitis, and hereditary angioedema.[9]

Mast cells are classified as granulocytic immune cells that are positioned in barrier organs and carry out proinflammatory and anti-inflammatory activities, utilising their ability to release a variety of mediators.[10] The important task of mast cells is the recognition of tissue injury, as they are closely associated with the epithelium and play an active role in the initial inflammatory response. Mast cells rely on receptors to detect tissue damage, leading to the release of mediators kept in granules, as well as the *de novo* production of these mediators. The activation of mast cells can happen via IgE receptors or via toll-like receptors, complement receptors, and IgG receptors. Mast cells have a unique role of repairing damaged tissue. Over time, mast cells reach the tolerance state, where the response to self-antigens and auto-immune antibodies levels to baseline.[11]

The progenitors of mast cells are haematopoietic stem cells. Mature, highly granulated mast cells have a *KIT* gene and receptor which are present in almost all tissues. KIT receptors undergo stem cell factor binding, and are not found in the blood stream.

In increasing numbers of patients, aberrant mast cell activation has led to a range of symptoms in the absence of systemic mastocytosis or antigen-specific mast cell disease. Systemic mastocytosis, in the World Health Organization (WHO) reclassification,[12] represents a rare genetic disease, characterised by the activation of mast cells with aberrant proliferation, leading to multiorgan symptoms and, in some patients, severely debilitating symptom burden.[13]

Mast cell activation syndrome is a more prevalent, heterogeneous condition with an unclear aetiology, but has clinically similar symptoms[14] associated with an impaired tolerance of mast cells.[15] The ethology and mechanisms of chronic mast cell dysregulation are not well understood, with many clinical studies emphasising the role of the epithelium or the presence of acute inflammation, which leads to mast cell activation.[16] The proposed mast cell activation syndrome diagnostic criteria are based on detecting the increased levels of mast cell mediators, as well as the treatment response with mast cell stabilising medications or therapies directed at interaction between released mast cell mediators and receptors.[17]

The overactivity of mast cells and subsequent parthenogenesis can affect the connective tissue. This can lead to the development of rare inherited diseases, such as Ehlers–Danlos syndrome.[18]

Histamine intolerance is often attributed to mast cells but, in fact, is not directly linked with any abnormalities of mast cells. This condition is associated with disorders of the digestive tract due to the reduction in activity of the diamine oxidase (DAO) enzyme, which is responsible for degradation of histamine within the gastrointestinal system.[19]

HISTAMINE AND DIAMINE OXIDASE

Histamine was discovered over 100 years ago. Also known as 2-(4-imidazolyl)-ethylamine, it is produced as a result of the decarboxylation of histidine, and is the most well-known biological mediator that has been attributed to mast cells.[19]

This biogenic amine is released from intracellular storage vesicles of basophils and mast cells after stimulation, leading to nitric oxide synthesis.[20] Histamine can affect the gastrointestinal, cardiovascular, and respiratory systems, as well as the skin, as a result of the activation of histamine receptors 1 and 2 on smooth muscle cells, endothelium of blood vessels, and the bronchial tree.[21,22] This leads to vasodilation, vascular hyperpermeability, angioedema, and hypotension,[23-26] which correlates with histamine concentrations.[27] Elevated histamine levels, when mean histamine concentrations can rise to 140 ng/mL,[22] were shown to increase vascular permeability, lead to airway constriction due to effects on smooth muscle cells, and promote chemotaxis of white blood cells, thus playing a leading role in various forms of anaphylaxis or life-threatening angioedema.[28] Mast cell tryptase is a useful factor in confirming the diagnosis of anaphylaxis, and should be taken in all acute settings as soon as it is practical and upon recovery.[29]

An enzyme that degrades histamine, E.C. 1.4.3.6 human DAO (hDAO), is encoded by the *AOC1* gene.[30,31] As a homodimer copper-containing amine oxidase, hDAO is produced in the intestinal[32] and proximal tubular kidney epithelial cells,[33] and extra villous trophoblasts.[34] After secretion, hDAO binds in the lamina propria to the basolateral membranes. Serum hDAO degrades histamine at a mean concentration of 125 ng/mL, with a half-life of 3.4 min.[35]

MAST CELLS

Mast cells are found in all vascularised tissues, and are granulated effector immune cells with multiple functions.[36] They were discovered by Nobel Prize-winning physician Paul Ehrlich over 140 years ago as a part of the innate immune system maintaining the first line of immune defence.[1] Mast cells take part in many physiological and pathological processes. In addition to known proinflammatory roles in allergic reactions, they are important in angiogenesis and tissue repair.[2] Mast cell maturation can be influenced by location, leading to functional and phenotypical heterogenicity. They are important in host defence, homeostasis, innate and acquired immune functions, and immunoregulation. They also play a key role in IgE mediated antiparasitic response and atopy,[37] response to infections, systemic disorders, development of tumours, and disorders of cardiovascular system.[38]

Mast cells display tyrosine-protein kinase KIT (cluster of differentiation 117), the receptor for stem cell factor Fc ε receptor 1 (FcεRI), which is a high-affinity receptor for IgE and G protein-coupled receptors on the cell surface, including the Mas-related G protein receptor X2, which has been linked to CSU, atopic dermatitis, asthma, and other mast cell-related diseases.[36] The granules of mast cells contain vascular endothelial growth factor and fibroblast growth factor 2 angiogenic cytokines, which contribute to the regeneration of nerve fibres and wound healing.[39]

Mast cells can be usually activated by FcεRI, a high-affinity receptor that is connected to a specific IgE to define antigens through mechanisms not involving FcεRI. These mechanisms involve binding the cells to different ligands. In general anaesthetics, positively charged hydrophobic molecules of morphine and vancomycin, quinolone antibiotics, muscle relaxant atracurium, and rocuronium, all lead to a release of mediators.[40]

Subpopulations of mast cells M1 and M2 are being studied, and current data suggest that, in various pathological conditions, the two major subtypes could have different or even opposite functions.[41] Pro- and anti-inflammatory mediators[37] (biogenic amines such as histamine

and serotonin; lysosomal enzymes; proteoglycans such as heparin and chondroitin sulphates)[37] and proteases such as tryptase, carboxypeptidase, cathepsin G, serine S1, granzyme, chymase, and TNF-α[42] that are released by mast cells have important immunomodulatory functions in the barrier organs (the skin, lungs, and gastrointestinal tract).[43] Inflammatory mediators, released by mast cells, promote growth and differentiation of endothelial cells and fibroblasts. Mast cell granules are present within a lipid membrane, which fuses with the plasma membrane.[44] The activation of mast cells can lead to the secretion of extracellular vesicles, such as microvesicles; exosomes with a variety of biological properties, and can influence other cells, located either closely or at distance, and modulate the inflammatory response, allergic inflammation, tumour development,[45] physiologic processes, and the maintenance of tissue homeostasis.[46]

There is no data on mast cell deficiency, leading to the conclusion that the functions of the mast cells are vital for life. Therefore, the use of the results from ongoing research into anti-c-Kit monoclonal antibody treatments should be approached with extreme caution.[47]

DISORDERS ASSOCIATED WITH MAST CELLS

Mast cell-activated diseases cover a very heterogeneous range of mast cell-mediated conditions, including urticaria, angioedema, systemic mastocytosis, mast cell leukaemia, and mast cell activation syndrome.[48] Clinical distinction between systemic mastocytosis, hereditary α-tryptasemia, and mast cell activation syndrome is difficult due to overlapping symptoms and pathophysiology.[49]

Mastocytosis

The WHO classification of mastocytosis has placed it into two groups: cutaneous mastocytosis and systemic mastocytosis.[12]

Cutaneous mastocytosis is responsible for 80% of mastocytosis cases. They mainly affect the skin during childhood, and improve or resolve completely by adolescence.[50] Cutaneous mastocytosis is considered a benign, self-limited condition, with a generally favourable prognosis and spontaneous regression of symptoms at puberty. It is the most common mast cell disease in children, presenting as urticaria pigmentosa.[51]

Systemic mastocytosis is diagnosed in over 95% of the cases, and usually persists for a longer time due to a gain-of-function mutation in the *KIT* gene, resulting in abnormal proliferation of clonal mast cells in various organs.[52] The mutation is found in the gene coding *KIT* D816V tyrosine receptor kinase (cluster of differentiation 117),[53] and can lead to increased and prolonged activation of the mutated mast cells as a result of abnormal apoptosis and proliferation.[4]

The prevalence of systemic mastocytosis in Europe is 0.3–13.0:100,000,[54] affecting males and females equally with unknown incidence.[55] It can be more challenging to diagnose in adults as it can lead to multiple organ dysfunction, with a very heterogeneous clinical presentation when there is no skin involvement. A maculopapular monomorphic fixed exanthema (urticaria pigmentosa, the typical presentation of cutaneous mastocytosis in adults, can precede other clinical symptoms for many years) presents in over 90% of the cases and is associated with systemic involvement.[10] Brown-red maculopapular skin lesions, 0.5 cm in diameter with local redness, can be noted. Pruritus (Darier's sign) and urticarial swelling is associated with mast cell mediator release, which can be provoked by physical factors and co-factors.[56] Less favourable outcomes are predicted for advanced systemic mastocytosis, while almost normal life expectancy and excellent prognosis can be predicted for the most common forms of indolent systemic mastocytosis,[57] with a moderate mast cell accumulation in the bone marrow and other organs.[58]

In all types of systemic mastocytosis, gastrointestinal symptoms can occur. Patients present with flushing, hypotension, tachycardia, sudden attacks of diarrhoea, nausea, and vomiting.[14,59] When genetic trait hereditary α-tryptasemia (HαT) is present, there is a higher incidence of severe, life-threatening anaphylaxis in patients with systemic mastocytosis, especially in patients with IgE-medicated allergy, including a food, venom, or drug allergy.[60]

Based on the WHO diagnostic criteria for systemic mastocytosis, an essential test for this condition includes a bone marrow biopsy.[58]

Hereditary α-Tryptasemia

In 2016, Lyons et al.[61] described HαT as a new genetic condition that is associated with slightly elevated basal tryptase levels,[62] and characterised by extra copies of the α-tryptase encoding gene *TPSAB1*. The genetic diagnosis requires the analysis of the duplication of the *TPSAB1* gene, which can have a total number of five or more copies; however, the total number of copies for *TPSAB1* and *TPSAB2* in individuals who are not affected is four.[63] Unfortunately, such genetic testing is not yet routinely available in many genetic laboratories. The routine availability of a genetic test will help to identify a cohort of patients with this condition and study risks for severe anaphylaxis or development of systemic mastocytosis.[64] Patients with HαT display multiorgan symptoms of mast cell activation, which is common for mast cell activation syndrome and systemic mastocytosis; however, some can be completely asymptomatic.[65]

Mast Cell Activation Syndrome

Clinically, mast cell activation syndrome is an extremely heterogeneous disease, with aetiology and pathology that is still not fully understood, making the diagnostic process more difficult.[66] Current evidence suggests that mast cell activation syndrome is associated with a number of mutations in signal transduction proteins that pathologically stimulate activated mast cells, kinases, and receptors in different organ systems.[67] *KIT* D816V point mutation is typical in systemic mastocytosis, but is not present in mast cell activation syndrome.[68]

Mast cell activation syndrome is characterised by aberrant inappropriate release of mast cell mediators.[48] The suspected mechanisms lead to pruritus, pain, abdominal cramping, vomiting, nausea, and flushing include increased mast cell proliferation, accumulation of altered or mutated mast cells, and decreased apoptosis.[68] The symptoms, depending on the organ system involved, can mimic systemic mastocytosis.[67] Mast cell related symptoms may include wheezing and upper respiratory inflammation, sneezing, rhinorrhoea, hypotensive syncope, tachycardia, flushing, pruritus, urticaria and angioedema, dizziness, vomiting, abdominal cramps, gastritis, nausea, diarrhoea, fatigue, and impaired concentration.[69]

Patients with long-COVID often report other unspecific symptoms in addition to classical mast cell mediator-induced symptoms, including fatigue, unexplained weight loss, organ enlargement, musculoskeletal symptoms, depression, and reflux.[70]

Diagnosis of mast cell activation syndrome is difficult as it has an extremely heterogeneous symptomatology. It involves different organ systems, is based on clinical and immunohistochemical findings in biopsies, and laboratory parameters within the diagnostic criteria. Mast cell activation syndrome reoccurs episodically, with subsequent remissions and symptom-free intervals; however, these intervals often become shorter as the disease progresses.[67]

The most common type of EDS is hypermobile EDS, uniting disorders, which results in chronic constitutive tissue defects. Reactive mast cell activation was introduced to the scope of mast cell disorders,[66] however mast cells are not affected in all patients with hypermobile EDS.

Urticaria and Angioedema

Chronic urticaria and angioedema represents a significant burden in the healthcare system and society in general, as well as patients and their families.[71]

Although the pathogenesis of CSU and angioedema is not yet fully understood, they occur due to the release and effects of mast cell mediators following mast cell activation in the skin.[72] Recently, the causes of CSU and angioedema were defined as autoimmunity Type I (autoallergic CSU, with IgE autoantibodies to self-antigens) and autoimmunity Type IIb (with mast cell–directed activating autoantibodies), with the remaining cases due to unknown causes. At the present time, unknown mechanisms are relevant for the degranulation of skin mast cells.[73]

DISCUSSION

Mast cell pathology ranges from non-specific to specific activation of mast cells and degranulation. An immediate hypersensitivity reaction to IgE is the most well-known (Type I). It represents antiparasitic immune responses, as

well as hypersensitivity reactions when specific IgE produced against harmless antigens land on high-affinity FcεRI, which are expressed on mast cells. Crosslinking of two IgE receptors occupied with specific IgE to the same antigen leads to mast cell degranulation.

The release of mast cell mediators can lead to a wide range of effects, resulting in rhinitis, bronchospasm, urticaria and angioedema, and, in the most severe cases, anaphylaxis.

The treatment of mast cell disorders begins with medications affecting mast cells and their mediators. Antihistamines block the interaction of histamine receptors with histamine. Cromolyn sodium is a stabiliser of mast cells and can act on signalling proteins in the cell membrane and chloride channels, resulting in reduction of degranulation. Anti-IgE treatment is the centre of treatment for uncontrolled urticaria and angioedema.

Mast cells are very important as they maintain antiparasitic responses, play a role in tissue reparation, and maintain homeostasis of connective tissues; however, they also trigger hypersensitivity reactions and a range symptoms due to mediator release.

Due to high-speed developments in the field of mast cells, it is important to follow the WHO classification of mast cell diseases; diagnostic criteria, which includes evidence of mast cell mediator release; and clinical benefits of treatments.

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Flagellate Erythema: A Case of Shiitake Dermatitis and Review of Pathogenesis

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Abstract

Shiitake dermatitis is a rare eruption that is associated with the ingestion of uncooked shiitake mushrooms, resulting in a distinctive flagellate erythema. It was initially hypothesised that the mechanism of disease related to a toxic reaction to lentinan; however, recent evidence has suggested a potential allergic mechanism. The authors herein present a case of shiitake dermatitis and review the current understanding of pathogenesis of this condition and flagellate morphology. With an increase in consumption of shiitake mushrooms in Western society, shiitake dermatitis is expected to become more prevalent worldwide.

Key Points

1. The rare phenomenon of the self-limiting condition shiitake dermatitis comes from ingesting uncooked shiitake mushrooms; the condition results in distinctive flagellate erythema.

2. Contrary to the pathogenesis that shiitake dermatitis is due to a toxic reaction to the polysaccharide lentinan, recent evidence has proposed that it may instead point to an allergic mechanism.

3. The authors present the case of a 75-year-old male presenting with a mildly pruritic, linear erythematous eruption, and flagellate erythematous plaques on their abdomen, upper back, neck, and scalp.

INTRODUCTION

Shiitake mushrooms (Lentinus edodes) are often used in Asian cuisine, with shiitake dermatitis first recognised in East Asian countries. Only recently has it become reported in Europe and other Western countries, correlating with a shift to more diverse cuisines worldwide.[1,2] Consumption of raw or undercooked shiitake mushrooms can lead to shiitake dermatitis with a distinctive erythematous eruption. This is characterised by the flagellate morphology, typically arranged in linear patterns involving the trunk and extremities. The underlying pathogenesis is currently poorly understood. It was initially hypothesised that the mechanism of disease related to a toxic reaction to lentinan; however, recent evidence has suggested a

potential allergic mechanism.[3] The authors herein present a case of shiitake dermatitis.

CASE REPORT

A 75-year-old male presented with a 1-day history of a mildly pruritic, linear erythematous eruption. He was otherwise systemically well. His past medical history was unremarkable, with no regular medication use. On examination, there were flagellate erythematous plaques coalescing over the abdomen and upper back, involving the neck and posterior scalp (Figures 1 and 2). There was no dermatographism, mucosal involvement, joint tenderness, proximal muscle weakness, or

Figure 1: Linear urticarial plaques from the upper back to the posterior scalp.

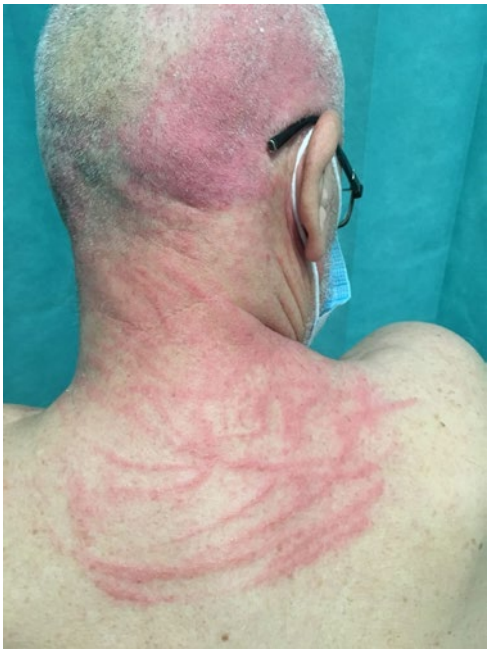
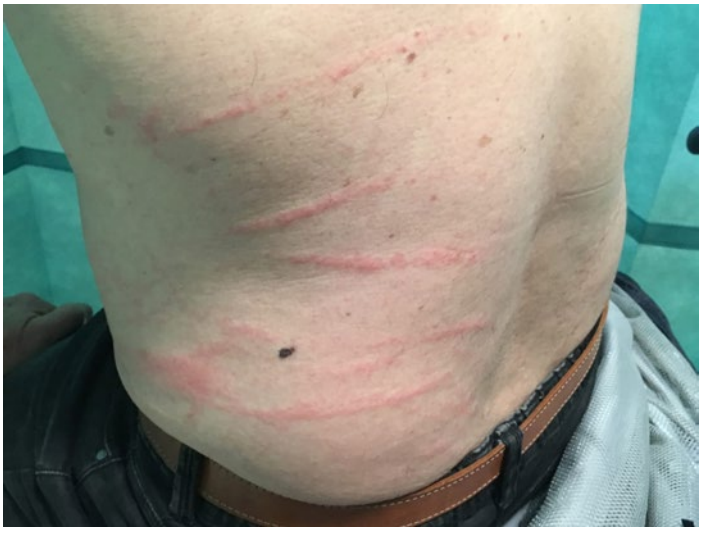


Figure 2: Linear urticarial plaques over the lower back.



other examination findings of dermatomyositis. Skin biopsy showed focal spongiosis as well as superficial light perivascular chronic inflammation with rare eosinophils and neutrophils in the lumen of superficial vessels. The patient was unaware he had consumed shiitake mushrooms prior to onset of the eruption until he was shown photographs of the mushrooms. Based on his history and clinical findings, a diagnosis of shiitake flagellate dermatitis was made. This patient was treated symptomatically with anti-histamines, topical betamethasone dipropionate ointment, and advised to avoid eating undercooked shiitake mushrooms. On follow up, the eruption had completely resolved after 10 days.

DISCUSSION

Shiitake dermatitis is a rare and self-limiting condition that is thought to be a toxic cutaneous reaction to lentinan, a polysaccharide derived from shiitake mycelia.[4] The exact pathogenesis of shiitake dermatitis and its associated flagellate erythema remains controversial. The cutaneous eruption occurs in susceptible individuals after ingesting raw or undercooked shiitake mushrooms, resulting in consumption of active lentinan. Adequate cooking of shiitake mushrooms denatures lentinan. A toxic reaction to active lentinan mediated by IL-1 secretion, causing vasodilation and haemorrhage, was initially hypothesised as the mechanism of action.[5] Shiitake flagellate dermatitis was first described in Japan by Nakamura in 1977, where it was initially termed as a toxicoderma.[6]

Moreover, there are scant reports of patients with shiitake dermatitis having delayed positive skin prick testing, suggesting a potential delayed-type hypersensitivity mechanism to be part of the pathogenesis.[2,3,7] Lentinan has also been implicated as an allergen in a few reported cases of shiitake mushroom allergic contact dermatitis as well as in cases of allergic alveolitis following inhalation of spores from the shiitake mushroom.[7-9] The relatively low incidence of shiitake mushroom dermatitis in contrast to its widespread consumption as well as a lack of outbreaks in groups of people with exposure to shared mushrooms may be explained by individual susceptibilities or hypersensitivity rather than a solely toxic reaction to active lentinan.

The mechanism behind the distinctive flagellate or 'whip-like' morphology also remains unclear. The degree of pruritus is variable amongst reported cases, with often a delay between time of insult and lesion onset. While it has been attributed to Koebner phenomenon induced by scratch injury, it has been reported that flagellate lesions are not immediately elicited after scratching. It is proposed that minimal trauma during periods of high serum lentinan leads to local deposition and upregulation of relevant inflammatory mediators and neuropeptides.[10,11] It has also been postulated that photosensitisation by active lentinan may underlie the mechanism of disease; however, in the authors' case, the cutaneous eruption was not limited to sun-exposed areas.

The offending agent and potential allergen, lentinan, has been investigated for potential anti-tumour properties through enhancement of the host immune and complement systems. A Japanese study found that patients with gastric cancer receiving lentinan in combination with paclitaxel or cisplatin chemotherapy resulted in longer overall median survival compared to patients receiving chemotherapy alone.[12] Ongoing large-scale studies are required to better evaluate the biological properties of lentinan in modulation of the immune system.

Shiitake dermatitis is usually self-limited, resolving in 2–4 weeks with symptomatic pruritic management, including emollients, topical steroids, and antihistamines. Adjunctive photography during patient assessment may be useful to confirm the diagnosis and history of shitake mushroom consumption. Skin biopsy findings of shiitake dermatitis are non-specific, largely demonstrating spongiosis, papillary dermis oedema, and perivascular inflammatory infiltrate without vasculitis. Shiitake dermatitis, therefore, remains a primarily clinical diagnosis. Differentials for the characteristic eruption include bleomycin-induced flagellate dermatitis, dermatomyositis, and adult-onset Still's disease.[11]

CONCLUSION

Given the growing popularity and availability of diverse foods, cases of shiitake dermatitis may be expected to become more prevalent, and it is, therefore, important to recognise this condition

in patients presenting with this clinical picture. The underlying mechanism of shiitake dermatitis and the immune reaction to lentinan remain to be fully understood.

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COVID-19, The Frequent Use of Moist Wipes, and Multiple Allergic Sensitisations: A Case Report

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Abstract

During the COVID-19 pandemic, frequent handwashing and disinfection have exacerbated or caused skin diseases. This case report shows the simultaneous development of allergic contact dermatitis to Kathon CG (DuPoint, Wilmington, Delaware, USA), Euxyl K400, and fragrance mix I because of the frequent use of moist (baby) wipes during the pandemic outbreak. The sensitisation to multiple allergens was determined by patch testing, whereas the disease resolved after usage discontinuation of moist wipes. Notably, two COVID-19 pulmonary events anticipated the clinical sensitisation. This case demonstrates that changes in attitude and behaviour with concern to exposure intensity to moist wipes can induce a clinical response to many allergens.

Key Points

1. The escalation of hygiene measures during the COVID-19 pandemic led to frequent hand washing and disinfection procedures as a way to reduce the spread of coronavirus. Many considered the use of moist wipes an equally healthy alternative to handwashing when other means were not available.

2. There are several reports on hand erythema, scaling, burning, and fissures; all of which were classified as signs of toxic-irritant hand dermatitis. This case report shows multiple sensitisation to fragrances and preservatives.

3. The importance of specification of products' ingredients on labelling is necessary to facilitate the discovery of potential allergens and to reduce the risk of side effects.

INTRODUCTION

COVID-19, the pandemic of the 21st century, emerged in Wuhan, China, and swiftly became a global phenomenon.[1] As a result of the COVID-19 outbreak, the intensification of hygiene measures led to frequent hand washing and disinfection procedures.[2-5] Such hygiene practices have caused or exacerbated skin diseases, especially among healthcare workers. These include irritant, atopic, and allergic contact dermatitis (ACD).[3-6] The most common complaints were redness, dryness, itching, cracking, burning, flaking, peeling, and lichenification.[7] This case shows a multiple sensitisation to fragrances and preservatives because of the frequent use of moistened wipes during the pandemic outbreak in a patient who had two COVID-19 pulmonary events.

CASE PRESENTATION

Disease History, Examinations, and Treatments

A 66-year-old White male complained about erythema and itching of upper extremities during the recent month. The objective examination revealed diffuse erythema on dorsal surfaces of forearms sensible to vitro-pressure and confluent oedematous infiltrative lesions. The authors observed similar but less evident lesions in the lower legs. The patient appeared like indurated psoriatic lesions; however, the subject has been addressed to an allergist after the exclusion of psoriasis by a dermatological examination. The initial suspect was a psoriasiform drug reaction because of the treatment of additional pathologies mentioned below.

The patient had rheumatologic arthritis for a couple of decades. The therapy comprised TNF-α antagonist (etanercept biosimilar) for the recent half-year and magnesium supplements for the last month. The patient also took antihypertensive and coronary artery disease medicaments such as ezetimibe/simvastatin, cardioaspirin, and bisoprolol over the last 15 years; also, six stents were inserted. Tamsulosin was also taken for prostatic hypertrophy. The patient preferred lactose- and gluten-free diets. There has been no change related to the detergents used. The patient had no prior allergic pathologies, nor a history of other family members with allergies.

The increased levels of rheumatoid factor, C-reactive protein, and erythrocyte sedimentation rate confirmed an inflammatory and autoimmune response (data not shown). Ultrasound examination of upper extremities revealed minimal oedema on the right radio-carpal articulation, minimal effusion on the periarticular areas, and around attachment sites of tendons, with hypoechogenic images in their distal segments. The subject reported two severe COVID-19 events, and the radiologic examination showed diffuse ground-glass opacities in the subpleural pulmonary zones.

The patient was informed and given official consent about procedures of examination, diagnostic methods, and treatment medications (including risks and benefits). The discontinuation of recently introduced medicaments (from other caregivers) revealed no changes in health status. Then, the successful treatment with methylprednisolone (locally, twice daily) and decreasing dose of prednisone (orally, initial daily dose 20 mg) for 2 weeks suggested the presence of ACD. It was only at this point that the patient informed the authors about the present prominent lesions at the perianal and perineal zones similar to those observed before in the upper extremities (not under recent treatment with methylprednisolone [Table 1]). The imperative patch test (European Baseline Series, Chemotechnique Diagnostics, Vellinge, Sweden) revealed a sensitisation to fragrance mix I, Euxyl K400 (phenoxyethanol and methyldibromo glutaronitrile), and Kathon CG (methylisothiazolinone/methylchloroisothiazolinone [MI/MCI], produced by DuPoint, Wilmington, Delaware, USA), both 48 and 96 hours after their application (Table 2) and Figure 1). Balsam of Peru revealed a suspect 48 hours after application. Thus, an ACD is

Table 1: The timeline of historical and current information.

Antecedent history until 1 month before the initial visit with the allergist	The last month until the first visit with allergist: initial complaints' information	The first week after visit with the allergist	The second and third weeks after the first allergist examination	The final week of follow-up
Rheumatologic arthritis, treated recently by etanercept biosimilar Arterial hypertension and coronary artery disease under treatment with different medicaments (and stents' placement) Two severe pulmonary COVID-19 episodes	Erythema and itching in extremities (especially the upper ones) Introduction of magnesium supplements At the visit day: objective examination and magnesium discontinuation	No changes in health status Introduction of glucocorticoid therapy (See text)	Resolving of symptoms shown in extremities Information about perineal and perianal elements Patch testing and results (See text) Information's exchange about moist wipes (usage)	Discontinuation of moist wipes usage led to resolving the skin symptoms without further pharmacological therapy

Table 2: The positively tested allergens

The positively tested allergen	Interpretation after 48 hours	Interpretation after 96 hours
Fragrance mix I 8% (amyl cinnamal, cinnamyl alcohol, cinnamal, hydroxycitronellal, geraniol, eugenol, isoeugenol, oakmoss absolute)	++	++
Euxil K400 1% (methyl dibromo glutaronitrile)	+	+
Kathon CG 0.01% (methylisothiazolinone and methylchloroisothiazolinone)	++	++
Balsam of Peru 25% (about 25 substances)	+/-	-

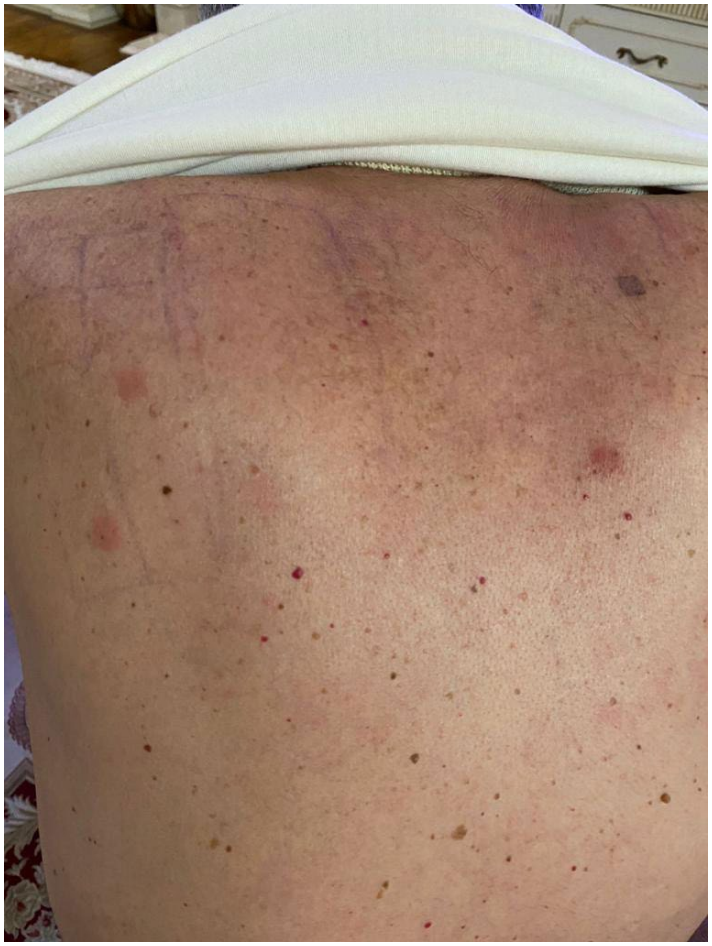
confirmed. The simultaneous patch testing for bisoprolol, aspirin, tamsulosin, and ezetimibe/simvastatin did not show sensitisation.

The authors informed the patient that the positively tested compounds are commonly present in the moisturised (baby) wipes. Afterward, the patient mentioned their frequent use for hygienic care of hands, forearms (even as a refresher), and perianal and perineal zones during the COVID-19 pandemic (even 1 day before the test interpretation). The source was not patched on the patient because the presence of the allergens was confirmed on the wipes used. According to the allergist's recommendations, the patient agreed to discontinue the usage of moist wipes and avoid other potential contactants and, 1 week later, the skin appearance had normalised without pharmaceutical treatment.

Differential Diagnosis

In the authors' case, morphological appearance and distribution mimicked psoriatic lichenification or lichen planus-like reactions, which belong to atypical manifestation patterns together with erythema multiforme-like reactions, bullous, nodular, granulomatous reactions, lymphomatoid reactions, etc.[8] The history of pharmaceutical

Figure 1: The positive patch testing (++) 96 hours after application (methyldibromo glutaronitrileon the left above; methylisothiazolinone and methylchloroisothiazolinone on the left below; and fragrance mix I on the right).



treatment suggested a cutaneous adverse drug reaction that, depending on its severity, may also mimic ACD. Based on the distribution pattern to contact localisation, simulators of ACD include psoriatic lesions induced by mechanical or chemical triggers, irritant contact dermatitis, dermatitis artefacta, Norwegian scabies, etc.[8] Their exclusion happened in accordance with the (in)effectiveness of mentioned medical measures.

DISCUSSION

General Considerations

Since the outbreak of COVID-19, authorities have preached the importance of personal hygiene, including handwashing and disinfection.[5] The COVID-19 pandemic has led to a significant increase in the incidence of signs of irritant hand eczema, since most of the affected subjects reported erythema, scaling, burning, and fissures that were classified as predominant signs of toxic-irritant hand dermatitis rather than contact allergy.[3] Of the populations who had never had hand eczema, a consistent proportion of studied subjects developed the pathology after returning to day care, showing a significant association with the frequency of handwashing or disinfection.[4,5]

The general population considers the use of moist wipes an equally healthy alternative to handwashing when other means are not to be disposed of. Yet, the first ACD case caused by moist toilet wipes was reported in 1980 and was related to a fragrance.[9] The incidence of ACD

to their ingredients has exploded over the last decades of the 20th century.[9-12]

According to the literature, the most frequent allergenic ingredients in moist wipes are preservatives and fragrances.[9] Among them, the allergy caused by preservatives shows more prominence than fragrance-induced allergy. Like our case, allergic contact perianal dermatitis because of a specific fragrance, cinnamic alcohol, was reported in a woman.[9] Both Fragrance mix and Balsam of Peru contain some common substances like different cinnamates or eugenol, which often can lead to double positivity.[13] In our case, the early positive response to both allergenic substances reflects this commonality, even not as a principal response.

Yet, the most problematic allergens in moist toilet wipes are preservatives. In the past, the most common allergen was the complex MI/MCI, also known as Kathon CG.[9,11,14,15] There were high sensitisation rates to MI/MCI in Europe, because of its widespread use in cosmetic products.[9-11,16-18] The negative publicity on the cosmetics preservative MI/MCI has made many cosmetic manufacturers look for safer alternatives.[14,15] The most popular substitute is Euxyl K400. Unfortunately, this preservative also induces allergic reactions to cosmetics and to 'moist toilet wipes', being thus, a growing problem.[10-12,14,15] According to the literature, the perianal and perineal occurrence of eczema should suggest an allergy to methyldibromo glutaronitrile and MI because of exposure to moistened toiled tissues.[12,14,16-18] Together with perianal and perineal zones, the regular usage of moist wipes by positive patients induces almost allergic and irritative symptoms in the hands and lower legs.[11,16,18] The lower lesions' intensity on the lower legs suggests an occasional contact with culprit allergens. Besides the reaction to baby wipes and moist towelettes, a minority of MI-positive patients reacted to MI in shampoos, conditioners, deodorants, moisturisers, etc.[18]

Case Details

Considering the moist wipes as a healthy hygienic instrument, the authors' patient used them for refreshing the affected forearms, without suspecting the deterioration of the situation. Patch testing revealed the simultaneous allergic sensitization at least to a fragrance (contained in the fragrance mix I), and at least in two different preservatives (contained in MI/MCI and Euxyl K400). To the authors' best knowledge, this is the first report of a triple sensitisation that causes ACD to allergens mentioned above. The sensitisation happened only after extensive use of moist wipes because of the COVID-19 pandemic. Like other reports, their usage discontinuation resolved the ACD.[16,17] Both fragrances and preservatives are of evident relevance to ACD, as suggested by patch testing results, and the knowledge that many sorts of moist wipes (used in the authors' country Albania) contain fragrances.

Other differential diagnoses we considered include COVID-19 infection-related immunological cutaneous eruptions and TNF-α-induced psoriasiform eruption. Severe COVID-19 has an immense effect on the immune and neuropsychological systems and, therefore, can trigger additional pathological situations. Rheumatoid arthritis and, especially, the use of TNF-α antagonists may induce psoriatic manifestations.[19,20] However, such manifestations cannot be resolved quickly after usage cessation of moist baby wipes.

Originating from a case report, these findings show the effectiveness of patch tests and allergens avoidance, as well as the limitation of the missed study sample. The final diagnosis (ACD) replaced psoriasiform drug reaction after partially successful treatment with glucocorticoids when the patch testing resulted positive for the allergens mentioned above. Afterward, the patient and their allergist exchanged information about the allergens' exposure and hygienic attitudes concerning moist wipes. The consecutive discontinuation of their usage led to skin normalisation (both the resolving of erythema and itching confirmed by the patient too). Collectively, these facts were the ultimate proof of ACD.

CONCLUSIONS

This case shows that the use of moist wipes causes a simultaneous clinical sensitisation to at least three quite different allergens, which can affect all the body zones exposed to. The changes in hygienic attitudes because of the

COVID-19 pandemic and an inevitable increase in exposure intensity to them can initiate a clinical response. Consequently, the specification of products' ingredients on their labels is necessary to facilitate the discovery of a potential allergen and to reduce the risk of side effects caused by culprit allergens.

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