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EMJ Allergy & Immunology

Review of EAACI Congress 2023

Editor's Pick

Drug-Induced Thrombocytopenic Purpura: A Systematic Review and Meta-analysis of Case Reports

Interview

Stefano del Giacco and Mohamed Shamji share insights into the EAACI 2023 Congress

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

I am delighted to welcome you to the 2023 issue of *EMJ Allergy & Immunology*. As always, this issue covers the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress, which took place in Hamburg, Germany. This year's congress theme focused on pathways from precision medicine to personalised healthcare in allergy and asthma. We have selected content from the congress to bring you the key highlights, which range from new treatment approaches for allergic rhinitis to new immunotherapy approaches to melanoma.

Amongst the many engaging sessions was one that focused on the new guidelines for the diagnosis of food allergy, the accuracy of diagnostic tests, and recommendations for practice. The guidelines are due to be published soon, so until then, you can read through a summary of the presentation on these guidelines in a short feature article.

We are proud to also bring you insights from two key experts we had the pleasure of interviewing at the EAACI Congress, as well as an expert paediatric allergologist discussing key advances and future directions in the field.

Our Editor's Pick for this issue includes an insightful review of drug-induced thrombocytopenic purpura, examining case reports of this condition, and highlighting the importance of early detection. You might also be interested in a narrative review of the biologic agents that inhibit IL-17 or IL-23 in people with moderate-to-severe psoriasis.

I would like to close by thanking our Editorial Board, contributors, and peer reviewers for helping bring together this high quality issue. The EMJ team is looking forward to welcoming your submitted manuscripts over the next few months, and we are already excited about next year's EAACI Congress!

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1) Bartosik, T. et al. (2022). J Allergy Clin Immunol Pract 10(7): 1889-1902 e1889.
2) Bergmann K.-C. et al. (2021). Allergo J Int 30(4): 141-149.
3) Bergmann K.-C. et al. (2022). Allergo J Int 31(6): 161-171.

Foreword

Dear Colleagues,

Welcome to the latest issue of *EMJ Allergy & Immunology*. As a doctor practicing in the field of allergy, I believe that it is important to validate our ways from time to time, especially with the arrival of new technologies, which are becoming increasingly present, and more expensive.

It is interesting to see that skin tests still have a space in medical practice, with a high level of sensitivity and specificity, but are low cost compared with other tests. Their rapid response allows us to immediately discuss therapeutic options with patients, without having to follow up later. However, I understand that this not always easy to obtain in many situations, and additional tests are necessary.

The European Academy of Allergy and Clinical Immunology (EAACI) Congress 2023 was held in Hamburg, Germany, from 9th–11th June, and virtually. It brought together dedicated healthcare professionals from around the world, and offered a unique opportunity to share knowledge and to learn from ever-evolving science.

The environment was the focal point this year. We are increasingly recognising the importance of this in the pathogenesis and motivations of therapeutic responses, especially with climate change. Early skin problems and knowledge of the defence mechanisms related to it allow us to understand its impact.

I cannot ignore the update on studies showing whether food allergy vaccinations work, which, as we know, is a hot topic. New diagnostic and therapeutic options were presented, and the education and interdisciplinary approach was emphasised.

EAACI 2023 has been most exemplary and, like you, I look forward to seeing the practical benefits in our daily lives. Next year's congress is set to be in Valencia, Spain.

I hope you enjoy this issue of *EMJ Allergy & Immunology*, and thank you to everyone who contributed to this publication.

Jacques Bouchard, MD

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

EAACI 2023

Review of the European Association of Allergy and Immunology (EAACI) Congress 2023

Location:	Hamburg, Germany
Date:	9th–12th June 2023
Citation:	EMJ Allergy Immunol. 2023;8[1]:10-15. DOI/10.33590/emjallergyimmunol/10307459. https://doi.org/10.33590/emjallergyimmunol/10307459.

This year's European Association of Allergy and Immunology (EAACI) Hybrid Congress was held in-person, in the beautiful historic city of Hamburg, Germany, and online. The largest congress in the field, with the greatest number of participants since before the onset of the COVID-19 pandemic, brought together 7,400 delegates on site, and many more virtually. Hamburg proved a fitting site for EAACI 2023, as it is a renowned location for research in allergy and immunology, and serves as a hub of innovation in the field.

EAACI President, Stefano Del Giacco, began the inaugural address as follows: "I am struck by the immense diversity of expertise and knowledge, which is represented in this room, and at this congress," and declared that EAACI is "more alive than ever," with 15,700 societal members.

The focus of EAACI 2023 was precision medicine in treating allergies and immunological diseases as effectively as possible. Plenary research sessions covered "every scientific track in the field of allergy and immunology," including the role of the microbiome in asthma, molecular allergology, and allergies in the paediatric population. Del Giacco gave an overview of the programme, stating that the congress would offer the latest developments in endotyping asthma and allergic diseases; novel analytical tests; the role of microbial immune response; and skin immunology, including new breakthroughs in IgE-mediated autoimmunity and the development of allergen immunotherapy.

Both Del Giacco and EAACI Vice President of Congresses, Mohamed Shamji, highlighted the importance of tailored healthcare for patients. As Shamji declared, it is of the utmost importance that EAACI can "move forward in a more personalised approach for diagnosis, treatment, and management" of allergic and immunological diseases.

The key EAACI achievement over the past year, as stated by Shamji, was the launch of the online EAACI Knowledge Hub, which brings together information about all of the recent developments in the field, as well as the opportunity to engage with experts. Shamji pointed to the huge contribution that the Knowledge Hub makes to the field, giving access to educational models, EAACI's own journals, and congress content, all on a single platform.

A keynote speech, entitled 'The Art of Observation and the Observation of Art', was given by Salvatore Mangione, Thomas Jefferson University, Philadelphia, Pennsylvania, USA. Throughout this fascinating introductory session, Mangione aimed to revisit "the roots of our profession."

During the Awards ceremony, five new EAACI Fellows were announced: Susanne Lau, Charité – Universitätsmedizin Berlin, Germany; Carsten Bindslev-Jensen, Odense Research Center for Anaphylaxis (ORCA), Denmark; Adnan Custovic, Imperial College London, UK; Pascal Demoly, University Hospital of Montpellier, France; Jeroen Buters, Technical University of Munich (TUM), Germany; and Cristobalina Mayorga, Instituto de Investigación Biomédica de Málaga (IBIMA), Universidad de Málaga, Spain.

The Clemens von Pirquet Award for Clinical Research was given to Marta Ferrer, Universidad de Navarra School of Medicine, Pamplona, Spain; the Daniel Bovet Award for Treatment and Prevention to Antonino Romano, Oasi Research Institute-IRCCS, Troina, Sicily, Italy; and the Paul Ehrlich Award for Experimental Research to Kari Nadeau, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA. Ignacio Dávila, University of Salamanca and University Hospital of Salamanca, Spain, was given the Charles Blackley Award for Promotion of the Specialty in Europe; Milena Sokolowska, University of Zurich (UZH), Switzerland, was awarded the prestigious Pharf Award; and Marine-Alexia Lefevre, University Hospital of Saint-Étienne, Loire, France, received the AllergoPharma Award.

EAACI also incorporated the Beat Allergy charity run into the 2023 Congress, to raise funds for friends and colleagues in Türkiye and Syria, who have been affected by two devastating earthquakes that occurred in February.

The EMJ team was thrilled to be a part of EAACI's 2023 congress, and is looking forward to next year's, which will be held in Valencia, Spain, between the 31st May–3rd June. This issue of *EMJ Allergy & Immunology* includes summaries of the most noteworthy press releases and abstracts presented at EAACI 2023. Read on for more insights from this year's congress.

"The focus of EAACI 2023 was precision medicine in treating allergies and immunological diseases as effectively as possible."

Allergen Exposure Chamber Assesses House Dust Mite Allergen Immunotherapy Outcomes

USE of an allergen exposure chamber (AEC) in the assessment of clinical outcomes of house dust mite (HDM) allergen immunotherapy (AIT) for patients with allergic rhinoconjunctivitis was validated in a study presented at the EAACI Congress 2023. This chamber allows patients to be exposed to the allergen in a controlled environment, under well-regulated and stable conditions.

In total, 50 patients were included in the study, which evaluated the efficacy and effectiveness of AEC-derived clinical outcomes of subcutaneous HDM AIT. All participants had HDM-triggered allergic rhinoconjunctivitis, confirmed through a variety of diagnostic tests, including serum-specific IgE, skin prick tests, and basophil activation tests. Patients were first assessed in the AEC before commencing AIT, then 12 months after treatment. The researchers assessed the effectiveness of AIT through multiple clinical endpoints, including visual analogue scale and total nasal symptom score, as well as objective parameters, including nasal secretion weight, peak nasal inspiratory flow, and acoustic rhinometry.

The team noted a statistically significant reduction in total nasal symptom score 12 months after treatment, as well as a high reduction in nasal symptoms, showing that the treatment had a positive impact on nasal symptoms.

Researchers concluded that the AEC challenge is safe, effective, reproducible, and consistent, allowing researchers to collect high-quality data quickly, and assess outcomes of HDM AIT in patients with allergic rhinoconjunctivitis. Furthermore, the findings suggest that the AEC could be an alternative to traditional trial designs, as the obtained clinical measurements align with the effectiveness evaluation through the Combined Symptom and Medication Score (CSMS) in real-life conditions. This study also suggests that accelerating dose escalation of native HDM AIT is convenient and safe. Further research is now attempting to validate clinical endpoints through immunological biomarkers, which could improve diagnostic and treatment approaches.

"This chamber allows patients to be exposed to the allergen in a controlled environment, under well-regulated and stable conditions."

New Immunotherapy Could Trigger Immune Response in Malignant Melanoma

IMMUNE responses can be triggered by IgE immunotherapy when treating malignant melanoma, according to research presented at the EAACI Congress 2023. Researchers from King's College London, UK, and Guy's and St Thomas' NHS Foundation Trust, London, UK, investigated the efficacy of a novel antibody to target and treat melanomas.

The most aggressive form of skin cancer, malignant melanoma has low survival rates. Although progress has been made in developing new immunotherapies that use an individual's natural defence system to fight the cancer, many patients fail to respond to current treatments. However, newly discovered antibodies could benefit patients with melanoma who do not respond to treatment.

Researchers have designed an IgE antibody that specifically targets immune responses towards melanoma cells. It was developed for chondroitin sulfate proteoglycan 4 (CSPG4), a marker that is found on the surface of human melanoma cells in up to 70% of cases.

Current immunotherapies use the IgG antibody, which broadly activates the immune system. However, the researchers illustrated how CSPG4 IgE can attach to and activate immune cells, effectively killing melanoma cancer cells, in the blood of patients with melanoma. Cancer growth slowed down when treated with CSPG4 IgE. Further, the researchers proved that CSPG4 IgE did not activate basophils, a type of white blood cell, in an allergy test. This result suggests the potential safety of this therapy.

> **"The most aggressive form of skin cancer, malignant melanoma has low survival rates."**

Previously, King's College London generated an IgE antibody to treat ovarian cancer, with the findings due to be published later this year. Heather Bax, King's College London, stated: "Our findings replicate existing observations for MOv18 IgE, the first anti-cancer IgE, which targets ovarian cancer, and supports development of IgE therapies for other solid tumours."

Researchers from both institutions were "excited about the prospect of a whole new class of antibody drugs in oncology," according to James Spicer, King's College London, and Guy's and St Thomas NHS Foundation Trust. ●

Potential New Treatment Approach for Allergic Rhinitis and Rhinoconjunctivitis

RESULTS of a randomised controlled trial evaluating the efficacy of Pollinex Quattro (PQ) Grass, a novel modified short-course subcutaneous immunotherapy, in treating allergic rhinitis and rhinoconjunctivitis were presented at the EAACI Congress 2023, in Hamburg, Germany.

Allergic rhinitis and rhinoconjunctivitis are common chronic inflammatory allergic conditions that affect the upper respiratory tract. Unlike currently used treatment strategies that target symptom control, allergen immunotherapy has shown potential in inducing clinical and immunological tolerance.

Following results from a previous Phase II study, researchers conducted an exploratory Phase III trial, utilising an adaptive trial design, and recruiting patients from 14 different sites in Germany and the USA. The aim was to evaluate the effectiveness of PQ Grass compared with placebo in addressing unmet needs of allergic patients by evaluating patient combined symptom and medication scores, averaged over the peak grass pollen season. Patients were randomised into four different treatment groups: PQ Grass conventional regimen, PQ Grass extended regimen, active placebo, or saline.

Mohamed Shamji, EAACI Vice President of Congresses, and Faculty of Medicine, National Heart and Lung Institute, Imperial College London, UK, and colleagues found that the combined symptom and medication scores were significantly improved in both the PQ Grass extended regimen and PQ Grass conventional regimen groups compared with placebo, with relative risk reductions of 39.5% and 33.1%, respectively. The absolute reduction in symptoms compared with placebo were 0.67 points for PQ Grass extended regimen and 0.56 points for PQ Grass conventional regimen. Furthermore, the PQ Grass extended regimen showed significant improvement in the total combined score.

> **"The PQ Grass extended regimen showed significant improvement in the total combined score."**

Shamji stated: "These findings highlight the potential of PQ Grass as an effective therapeutic option for allergic patients. The adaptive trial design utilised in this study enables a more efficient evaluation of treatment strategies, providing valuable insights into the clinical and immunological effects of novel therapies." Whilst these results are promising, PQ Grass is not yet approved, and further studies to determine the safety and efficacy are required. ●

Urticaria and Beyond

Authors: Evan Kimber, EMJ, London, UK

Citation: EMJ Allergy Immunol. 2023;8[1]:16-18. DOI/10.33590/emjallergyimmunol/10307200. https://doi.org/10.33590/emjallergyimmunol/10307200.

HONING in on urticaria and other mast cell driven diseases, experts at the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2023 presented a forward-thinking session in one of the most insightful symposia from the hybrid meeting hosted in Hamburg, Germany. Feeding into the over-arching congress motto, "pathways from precision medicine to personalised healthcare in allergy and asthma," the speakers outlined what the future holds for targeting cells and identifying remission, amongst other topics in this field.

TARGETING MAST CELLS

There are many mast cell targeting drugs currently available, and Martin Metz, Charité – Universitätsmedizin Berlin, Germany, began by presenting these alongside the many more drugs in development and in ongoing clinical trials, which are likely to become available soon. Metz arranged these treatments into four main categories: those that block mast cell mediators, inhibit mast cell activation, silence, and deplete mast cells.

Presenting data for three different modes of action: remibrutinib targeting Bruton's tyrosine kinase, barzolvolimab targeting KIT, and dupilumab targeting IL-4 receptor, Metz promised that there is much more to come, and outlined future applications for urticaria. Describing the surprising efficacy of dupilumab as a drug for urticaria, Metz expressed that, "we have to rethink the role of mast cells in many diseases and see the targets on these cells as being interesting in mast cell-driven diseases." They went on to describe the biology behind barzolvolimab as a "super fascinating" drug, depleting mast cells through encouraging apoptosis and producing symptom-free patients.

Looking beyond urticaria, Metz offered insight into the future applications for the targeting of mast cells. Mastocytosis and mast cell-activation syndrome were among the first and most direct pathways to explore.

Metz went on to provide an extensive list where there is evidence that targeting therapy could be helpful, ranging from asthma, psoriasis, and rheumatoid arthritis to inflammatory bowel diseases, migraine, and autism spectrum disorder. This presentation confirmed there are multiple inter-specialty avenues to explore where the role of mast cells is not yet clearly defined.

> **"Metz offered insight into the future applications for the targeting of mast cells."**

IDENTIFYING REMISSION AND DISCONTINUING TREATMENT

Massimo Triggiani, Università degli Studi di Salerno, Italy, began by acknowledging the complex and heterogeneous mechanisms that are involved with the common clinical conditions chronic spontaneous urticaria (CSU) and angioedema. Triggiani went on to define 'control' and 'remission' for CSU, differentiating between the two as an absence of disease during treatment, and 6 months after the treatment ceased.

Triggiani underlined that attempts to stop CSU treatment when the disease is well controlled should always be made.

The presentation touched on the methods for assessment of control, recommending that clinicians undertake frequent and specific disease evaluations with their patients, alongside questionnaires for patient quality of life. Triggiani shared the criteria for complete, good, partial, and absence of control, referencing several studies which have looked at the risk factors of CSU persistence and tracked clinical course. Triggiani acknowledged a gap in literature studying paediatric populations by discussing an investigation that compared male and female data on remission, and noted the interesting co-interaction of chronic urticaria in children with atopic dermatitis, allergic rhinitis, and asthma. A key point from this section was the finding that a high eosinophil count is a protective factor.

Presenting longitudinal data spanning 10 years from the Università degli Studi di Salerno, Triggiani spoke about the responsiveness of patients to antihistamines. Discussion then shifted to dermographism and its transient nature, detectable in about half of patients with CSU, and not usually associated with pruritis. "I do not know really if dermographies can be intended as a way to assess mast cell reactivity *in vivo*, was the honest statement that Triggiani opened to the floor, but they followed up by confirming that, "certainly, most of the patients that enter into remission, are patients who lose steadily their dermography characteristics."

Triggiani outlined the factors that are useful in predicting time to CSU remission, some with conflicting data and caveats. Data showed that female gender and the age of a patient were among the factors predicting a longer time to remission; the same was observed for a higher severity of CSU, longer duration of disease, and concomitant angioedema. More research is warranted on responses to antihistamines as the predictive value of this is unknown. The same is seen for eosinophilia and basopenia, but for total serum IgE the predictive value is limited.

"Triggiani outlined the factors that are useful in predicting time to CSU remission."

Triggiani finished their talk by bringing all the topics they had discussed together, with the help of a large study that employed machine learning to assess clinical remission. Triggiani recognised there is no full agreement on a definition for remission, but promoted this integrated analysis as an artificial intelligence model for predicting CSU recurrence. A real takeaway from this segment for clinicians was that patients should be informed that recurrence of urticaria is the rule rather than the exception, and reassurance should be provided that in the case of recurrence previous treatment will be as safe and effective as it was before.

CONCLUDING REMARKS

"The neglected duckling of urticaria," was the way Marcus Maurer, Charité – Universitätsmedizin Berlin, Germany, described chronic inducible urticaria when concluding this session. Maurer highlighted differences compared with CSU, its more common counterpart, and brought real energy to the stage providing guidance for physicians dealing with patients with this disease. Maurer encouraged development of better drugs for chronic inducible urticaria, advising threshold testing to assess disease activity, aiming for complete control until remission, and starting with non-sedating antihistamines.

Finally, Maurer recommended a higher than standard dose for patients, if required; omalizumab when antihistamines fail; and that patients are guided towards clinical trials.

The cutting-edge contributions in this session will have significant impact on the decision-making and practice of clinicians as they go back to their work, providing a satisfying 'itch' for those specialising in the field of and living with urticaria. What is clear from this talk is that although great advances are being made, there is a great deal to be uncovered still with this complex condition, as we move towards more precise medicine and provision of care.

EAACI Guidelines on Diagnosis of Food Allergy: What Is New?

Authors: Abigail Craig, EMJ, London, UK

Citation: EMJ Allergy Immunol. 2023;8[1]:19-21. DOI/10.33590/emjallergyimmunol/10307474. https://doi.org/10.33590/emjallergyimmunol/10307474.

AN ENGAGING session presenting the newly-revised European Academy of Allergy and Clinical Immunology (EAACI) guidelines on the diagnosis of food allergy, centred around the accuracy of diagnostic tests and recommendations for practice. The session, chaired by Alberto Alvarez-Perea, Maternal and Child Hospital Gregorio Marañón, Madrid, Spain, and Eva Untersmayr-Elsenhuber, University of Vienna, Austria, was presented at the EACCI Congress 2023 in Hamburg, Germany.

DIAGNOSTIC TEST ACCURACY IN IgE-MEDIATED FOOD ALLERGY

The previous guidelines, released in 2014, were based on a meta-analysis of papers published prior to 2013. Since then, there have been numerous advances, such as the widened availability of IgE testing and the development of novel techniques, such as the basophil activation test (BAT). In order to inform the updated guidelines, the research team completed a systematic review of all the diagnostic tests available for IgE-mediated allergy. This comprehensive study aimed to overcome the limitations of prior individual studies, ensuring the production of reliable, generalisable results. Carmen Riggioni, EAACI Food Allergy Guidelines Expert Group and EAACI Research and Outreach Committee Food Allergy Group, commenced the session by summarising the recent evidence, presenting and explaining the rationale behind the updated guidelines for the main IgE-mediated food allergies.

Studies investigating participants with suspected IgE-mediated allergy to any food were included, with the sensitivity and specificity of all index tests investigated. Importantly, each study was required to use an open food challenge (OFC) in a group of participants to generate a control. Overall, 149 studies, encompassing 24,489 participants, were included. The risk of bias assessment suggested a moderate level of heterogeneity in the studies, but overall, there was good applicability due to the use of OFC as a control.

The most accurate tests for each food allergy were summarised, with the optimal cut-offs defined in each included study analysed. This enabled the generation of median and interquartile range values for each diagnostic test. Peanut allergies were most commonly investigated by the included studies, enabling the identification of two tests that were highly specific for IgE-mediated food allergy: Ara h 2 and BAT. For Ara h 2, the median optimal value was defined as 0.44 kU_A/L, while the interquartile range was 0.30–1.30 kU_A/L, compared with a median optimal value of 5.0% and an interquartile range of 4.7–7.1% for BAT. Regarding raw egg, ovomucoid, skin prick test (SPT) with egg yolk, and SPT with ovalbumin were found to be the most specific tests, with median optimal cut-offs of 0.8 kU_A/L, 7 mm, and 10 mm, respectively. Cooked egg, ovomucoid, and SPT with ovalbumin remained accurate, with the addition of SPT with raw egg white; this is an interesting result, as allergists have been moving away from this test, more commonly opting to use extract. However, Riggioni emphasised that the results indicate that this is still a highly accurate, and thus valuable, test. Baked egg was less commonly investigated by the included studies, resulting in the generation of a broad interquartile range (6–50 kU_A/L) for IgE. Casein, SPT, IgE, and α-lactalbumin were found to be the most specific

tests for cow's milk; however, the research team were unable to perform a meta-analysis for baked cow's milk due to a lack of eligible studies. Cor a 14 and BAT were the most specific for hazelnuts and sesame, respectively, and in this case, BAT had low variability, suggesting modern tests are of a better quality. For wheat and soy, tests with good specificity and sensitivity were not identified. However, Riggioni suggested this is an expected result, since these allergies are very difficult to diagnose in clinical practice. With regards to shrimp allergy, SPT was the most sensitive. However, the included studies reporting SPT results were limited to shrimp extract, meaning these results cannot be extrapolated to the variety of SPTs used in clinical practice.

The research team then performed a subgroup analysis to ascertain whether previously defined cut-off values for different food tests remained accurate. For peanut allergies, a SPT value ≥8 mm and a specific IgE ≥15 kU_A/L still had high specificity. However, for egg allergy, the research team were unable to calculate the specificity of previously defined cut-off SPT and IgE values for egg white. Ovomucoid, on the other hand, remained specific, along with the cut-off values for SPT for cow's milk allergy and Cor a 14 for hazelnut allergy.

Riggioni then emphasised the importance of continued assessment of allergy test specificity, due to variability. For example, Ara h 2 has high specificity in Northern Europe (99%), Australia (97%), and Western Europe (92%), but in Asia the specificity is much lower (79%). Subgroup analyses, considering factors such as geographic location and age, were challenging, as included studies often failed to report this detail.

In conclusion, newly defined cut-off values for optimal sensitivity may be more useful in the screening and confirmation of the diagnosis of food allergy. Furthermore, there is strong evidence supporting the accuracy of SPT, specific IgE, and component-resolved diagnostics in aiding the diagnosis of peanut, cow's milk, egg, and tree-nut allergies. However, the diagnostic performance of the various tests is allergen-specific, and largely dependent upon the food being tested; thus, it is important to remember that no test is absolute.

"The diagnostic performance of the various tests is allergen-specific."

RECOMMENDATIONS FOR CLINICAL PRACTICE

Alexandra Santos, King's College London, UK, delivered the second talk regarding the EAACI guidelines update. This focused on how to implement the key updates in clinical practice, with the rationale and strength of each recommendation discussed.

Firstly, for patients with suspected IgE-mediated food allergy, a detailed allergy-focused history is recommended as the first diagnostic work-up. Key questions that need to be asked at this stage include age at symptom onset, presenting symptoms, reproducibility of reactions, and dietary history. Clinical history must be combined with the results of allergy tests to make an accurate diagnosis.

> **"A detailed allergy-focused history is recommended as the first diagnostic work-up."**

Following this, patients with a history of suspected IgE-mediated food allergy, SPT, and/or serum specific IgE are recommended as first-line tests for the diagnosis of food allergy. This is especially relevant to patients where a possible reaction has been reported, or there is epidemiological evidence of risk for a specific food allergy. Allergens tested should be directed by clinical history, ensuring panel testing is avoided wherever possible. Santos emphasised that the previously discussed cut-offs should act as a guide during diagnosis, reminding us that that they are not absolute.

The third recommendation refers to patients with suspect IgE-mediated allergy to peanut, hazelnut, or cashew nut. Ara h 2, Cor a 14, and Ana o 3, respectively, are recommended in this case, in conjunction to SPT and/or IgE extracts where available. This is most important when the history is unclear, or the results of SPT/IgE are insufficient for diagnosis. The expert panel, responsible for the guideline update, recommend concurrent testing for the component and the extract, to avoid false negative results.

It is also recommended that BATs are utilised in patients with an equivocal diagnosis of IgE-mediated allergy to peanut or sesame.

The previously discussed meta-analysis reported a high certainty of evidence regarding the value of BAT. In this case, however, it should be recognised that this testing is not available in most countries, and as such, the clinical recommendation is conditional.

Santos stressed the importance of the fifth recommendation: patients with suspected IgE-mediated food allergy should not receive the isolated use of IgG and IgG subclass tests. This is due to limited evidence, but also limited rationale for conducting these tests in clinical practice, due to ethical concerns, cost, and the unnecessary avoidance of allergens.

Recent evidence also suggests that children who have food allergies should be retested at regular intervals to test for spontaneous tolerance. Santos reminded the audience that younger children and patients allergic to milk, egg, wheat, and soya are more likely to develop spontaneous tolerance, both factors that should inform clinical decision making.

The penultimate recommendation refers to medically-supervised OFC. A high certainty of evidence suggests patients with an unclear diagnosis, despite IgE-sensitisation tests, should receive an OFC to confirm or exclude food allergy.

Finally, a double-blind, placebo-controlled food challenge (DBPCFC) is recommended only when an open OFC outcome is indeterminate. However, the certainty of evidence supporting this recommendation is low, due to a lack of studies comparing OFC with DBPCFC. The expert panel also acknowledge that an open OFC is valuable for most cases in clinical practice, while DBPCFCs should be reserved for research purposes, or for cases where subjective symptoms are expected, or the patient is highly anxious.

Santos concluded by outlining the recommended algorithm for the diagnosis of an IgE-mediated food allergy, developed based on the meta-analysis and recommendations outlined above.

CONCLUSION

Overall, these updates to the EAACI guidelines on the diagnosis of food allergy will help to optimise decision-making for physicians and healthcare professionals, contributing to improved patient care.

How Do Human Milk Oligosaccharides Modulate the Immune System in Infants with Cow's Milk Protein Allergy? Emerging Evidence and Clinical Implications

This symposium took place on 9th June 2023, as part of the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress

Chairpeople:	Alexandra Santos[1,2]
Speakers:	Liam O'Mahony,[3] Anna Nowak-Węgrzyn,[4,5] Ralf G. Heine[6]

1. King's College London, UK
2. Evelina London Children's Hospital, UK
3. Department of Medicine, School of Microbiology, APC Microbiome Ireland, University College Cork, Republic of Ireland
4. New York University (NYU) Grossman School of Medicine, New York City, USA
5. Hassenfeld Children's Hospital, NYU Langone Health, New York City, USA
6. Research & Clinical Development, Nestlé Health Science, Vevey, Switzerland

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Meeting Summary

During this symposium, leading experts in paediatric allergy and immunology examined evidence for the immunomodulatory role of human milk oligosaccharides (HMO) in infants with cow's milk protein allergy (CMPA), and considered the implications for clinical management. Mechanisms underpinning the positive modulatory effect of HMOs on the early microbiome and immune system responses in healthy infants and those with CMPA were explored by Liam O'Mahony, University College Cork, Republic of Ireland. Anna Nowak-Węgrzyn, Professor of Pediatrics at the New York University (NYU) Grossman School of Medicine, and Chief of the Division of Pediatric Allergy and Immunology at Hassenfeld Children's Hospital, NYU Langone Health, New York City, USA, then reviewed findings from the CINNAMON and PLATYPUS clinical trials, highlighting the beneficial impact of HMO-supplemented formula on the clinical management of infants with CMPA. In these studies, hypoallergenic formulae containing the two key HMOs, 2'-Fucosyllactose (2'-FL) and Lacto-N-neotetraose (LNnT), showed a good safety profile, supported normal infant growth, and, importantly, helped to reduce the risk of respiratory infection in children with mild, moderate, or severe CMPA. In the final presentation of the symposium, Ralf Heine, Global Medical Director of Paediatric Care at Nestlé Health Science, Switzerland, showcased new data from the CINNAMON and PLATYPUS studies, shedding further light on the mechanisms by which HMOs can shape the early microbiome and influence the metabolome profile associated with important immune benefits in CMPA.

Mechanisms of Human Milk Oligosaccharides in Modulating Immune Responses

Liam O'Mahony

Human mucosal surfaces and body cavities harbour diverse communities of commensal microbes that play essential roles in the regulation of host metabolic responses, epithelial barrier function, immune education and immunoregulation.[1] From a sterile beginning, infants acquire these key microbes via many routes, including maternal transmission, from older siblings, and via contact with the wider environment.[2] However, in the modern world, development of the early life microbiota can be hampered by factors such as Caesarean section delivery and antibiotic use, as well as smaller households and social network sizes.[2] Once microbes are acquired, they must also be supported by the diet, explained O'Mahony, with dietary elements such as HMOs playing a particularly vital role in early-life microbiome development.

The microbiome develops in concert with the early-life immune system, with both the composition of the microbiome and its metabolic outputs helping to co-ordinate and drive communication pathways between early immune cells. This enables effector and regulatory networks to be established within the immature immune system, the failure of which can result in allergy.

To illustrate the importance of diet for early-life microbiome development, O'Mahony presented results from an unpublished study showing that 20–25% of microbiome variance in children aged 6–12 months can be explained by diet alone, an impact far greater than Caesarean section delivery. The main standout dietary factor

contributing to a varied microbiome development in this study was breastfeeding. HMOs are one of the most important and abundant components of human breast milk, and over 150 different types have been identified. These complex sugars cannot be utilised by the human host, but instead are designed to support the growth and metabolism of protective commensal microbes, particularly infant-type bifidobacteria.

Many factors influence the HMO composition of a mother's breast milk, and the ensuing differences can have an important impact on outcomes, such as food allergy. Studies have shown that relative HMO levels in breast milk correlate with CMPA risk in offspring, mediated via HMO effects on the immune system.[3,4] The positive effect of HMOs also extends to infection risk, with supplementation of infant formula with the two key HMOs, 2'-FL and LNnT, shown to reduce the early-life incidence of bronchitis, lower respiratory tract infection, and antibiotic/antipyretic usage in otherwise healthy infants.[5]

Looking at the mechanisms by which HMOs act to positively modify allergy and infection risk, O'Mahony explained that HMOs exert both direct and indirect effects on the immune system. Indirect immune modulatory mechanisms include the expansion of immunoregulatory protective species, such as bifidobacteria, in the early gut microbiome.

Bifidobacterial strains have been shown to be important inducers of T regulatory cells in both mouse model experiments and human studies, an effect mediated via extracellular polysaccharides.[6-8] In animal studies, removal of these key immunomodulatory cell structures was associated with significant increases in levels of inflammatory mediators, such as TNF-α and eosinophils.[9,10] Bifidobacteria supported by dietary HMOs also play an important role in protection against infection. In a lethal influenza model in mice, just one intranasal application of bifidobacteria cell wall conferred a 50–60% increase in survival rates, accompanied by a significant reduction in viral titres versus placebo-treated animals.[11]

In addition to supporting the growth and metabolism of bifidobacteria, HMOs also act to modify microbial metabolism and generate key immune regulatory compounds in the early-life microbiome. As a result, infant metabolomic profiles are seen to change dramatically with HMO supplementation.[12] Important metabolites include the short-chain fatty acids (SCFA) acetate, propionate, and butyrate, which engage with host cell receptors, and also influence the immune system epigenetically via histone deacetylase inhibition.[13] Collectively, these effects induce an immune regulatory response, and protect against allergic sensitisation and viral respiratory tract infection. Higher levels of SCFAs in early life have been linked to a lower rate of sensitisation to both inhalant and food allergens at 6 years of age.[14] In terms of disease outcomes, children with higher levels of butyrate also displayed a lower prevalence of asthma, allergic rhinitis, and food allergy by the age of 6 years.[14]

Finally, HMOs also exert direct actions on epithelial cells and immune cell subsets within the mucosa. These effects include the prevention of pathogen adhesion and infection, modification of innate immune cell activity, and improvement of epithelial barrier function.

Human breast milk contains many immunomodulatory factors, of which HMOs are undoubtedly one of the most important, concluded O'Mahony. HMO effects can be direct or indirect, and help to steer the development of vital regulatory and effector networks within the early-life immune system.

Clinical Implications of 2'-Fucosyllactose and Lacto-N-neotetraose in the Nutritional Management of Cow's Milk Protein Allergy

Anna Nowak-Węgrzyn

CMPA currently ranks as the most prevalent food allergy in young children, with an incidence of 2–3% in the first year of life.[15] It is an immune-mediated disease characterised by immune system hyperactivity, increased gut permeability, and altered gut microbiota, giving rise to intestinal dysbiosis.[16-19]

Nowak-Węgrzyn explained that infants and children with CMPA have a higher risk of developing infectious complications, predominately lower respiratory tract infections

(LRTI), which is reflective of the T-helper (Th)1/Th2 imbalance and delayed immune system maturation.[20,21] The control and elimination of intracellular pathogens requires the activation of immune responses, which are often hampered in CMPA, thereby increasing susceptibility to these infections.[22] More infections equate to more oral antibiotics, Nowak-Węgrzyn continued, with those who have CMPA receiving an average of three courses in their first 3 years of life.[21]

HMOs, notably 2'-FL and LNnT, which are the most abundant in human breast milk, play a key role in supporting the infant immune system in CMPA. They promote beneficial bacteria, thereby protecting from dysbiosis associated with CMPA, and also boost gut barrier function to counteract CMPA-associated increased permeability.[17,18,23-26] In addition, HMOs block pathogen adhesion in the gut to protect against respiratory tract infections, and directly modulate the immune system, helping to rebalance the abnormal Th1/Th2 responses seen in CMPA.[17-20,23-25,27,28]

A new generation of hypoallergenic formula incorporates the two key HMOs, 2'-FL and LNnT, which are identical to those found in maternal breast milk. The hypoallergenicity of the whey-based, lactose-containing, extensively hydrolysed formula (w-eHF), supplemented with 2'-FL and LNnT (Althéra® HMO, Nestlé Health Sciences, Vevey, Switzerland) was confirmed in a multicentre clinical trial conducted in the USA.[21] In that study, children with CMPA, aged 2 months–4 years, were assessed by double-blind, placebo-controlled food challenges to HMO-supplemented w-eHF, or a currently marketed control w-eHF without HMO. Results showed that the percentage of subjects tolerating the test and control formulae was 98.4%, meeting clinical criteria for hypoallergenicity set out by the AAP.[21,29]

Nowak-Węgrzyn explained that this HMO-supplemented w-eHF was then further assessed in the CINNAMON study, a longer-term, double-blind, randomised, international, multicentre trial.[30] In total, 194 infants were randomised 1:1 to receive either the test or control formula and, by 4 months, the per protocol groups included 73 test and 64 control subjects, respectively. The primary objective of the CINNAMON trial was to determine if weight gain was appropriate with the HMO-supplemented w-EHF compared with the control w-eHF without HMO, given the former's reduced protein content.

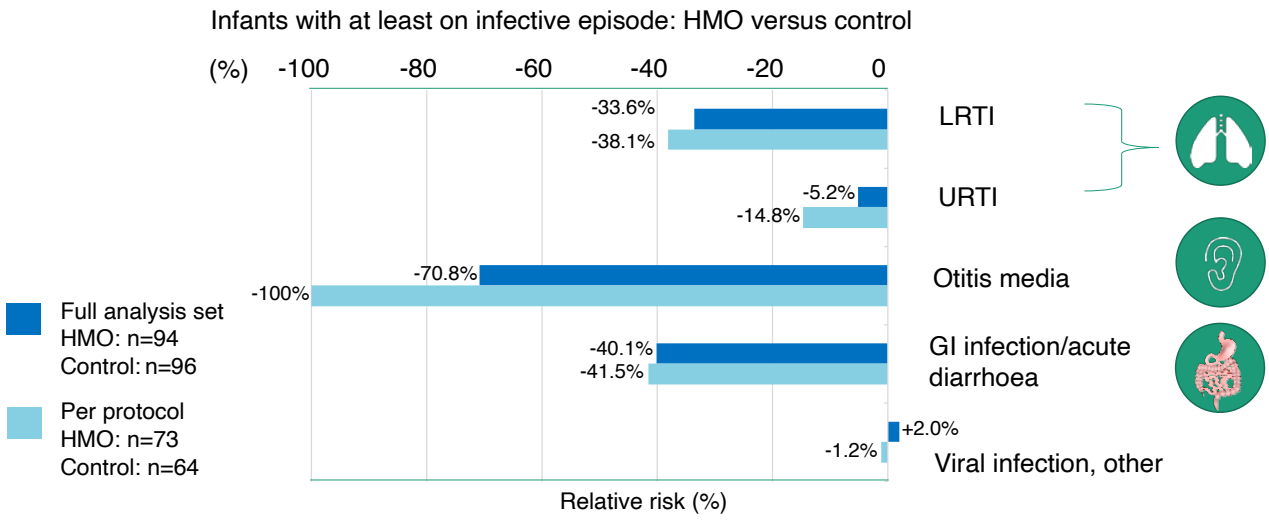
Results from the CINNAMON study were positive, with similar average daily weight gain for the test and control groups confirming the non-inferiority of the HMO-supplemented w-eHF, despite lower protein content. Adequate growth was achieved in both groups, with no differences in key parameters such as weight for age z-scores or length for age z-scores between the HMO-supplemented formula versus control. Comparison of the Cow's Milk-Related Symptom Score (CoMiSS™), which was used to track the symptom resolution across the time points of the study, also found no significant differences between the test and control group.[30]

Assessed as a secondary outcome in the CINNAMON study, Nowak-Węgrzyn described the impact of 2'-FL and LNnT supplemented w-eHF on infective morbidity as "very interesting." From enrolment in the CINNAMON study to 12 months, a relative risk reduction was seen for various infections in infants fed the supplemented formula (Figure 1).[30]

Notably, there was a statistically significant reduction in the monthly frequency of upper respiratory tract infections (URTI) in the HMO-supplemented group versus control, together with a decreased incidence of ear infections at 12 months in the per protocol group.[30] A non-significant, but clinically relevant, trend of 30–40% relative risk reduction in LRTI and gastrointestinal infections was also seen in those infants fed 2'-FL and LNnT-supplemented w-eHF.[30]

Nowak-Węgrzyn pointed out that these findings are in keeping with the reduced incidence of respiratory and gastrointestinal infections observed in healthy infants receiving HMO-supplemented standard infant formula. For example, one study revealed a significant 44% relative reduction in the risk of LRTIs in healthy infants fed formula with 2'-FL and LNnT from 2 weeks–12 months of age.[5] Although the results for LRTIs in the CINNAMON study did not reach statistical significance due to sample size limitations, a 23% reduction in LRTI frequency per month was observed in infants with CMPA fed the supplemented formula. However, the study reported a highly statistically significant (p=0.003) 42% reduction in URTI episodes

Figure 1: Relative risk reduction in infections (baseline to 12 months) in the CINNAMON study.[30]



Adapted from Vandenplas Y et al.[30]

EAACI: European Academy of Allergy and Clinical Immunology; GI: gastrointestinal; HMO: human milk oligosaccharide; LRTI: lower respiratory tract infection; URTI: upper respiratory tract infection.

per month.[30] The positive impact of HMO-supplemented w-eHF on URTI frequency is particularly important, stressed Nowak-Węgrzyn, because these are the infections driving unnecessary use of oral antibiotics in early life, and worsening gut dysbiosis.

Overall, the CINNAMON trial showed that 2'-FL and LNnT supplemented w-eHF formula supported normal growth, was effective at resolving allergy symptoms within 1 month, and led to infection reduction in infants with CMPA. This study suggests that Althéra® HMO has immune-enhancing properties, conferring a protective effect against respiratory and ear infections in infants with CMPA.[30]

Nowak-Węgrzyn went on to present results from the PLATYPUS study, which compared the growth of infants with moderate-to-severe CMPA fed an amino acid-based formula (AAF) containing 2'-FL and LNnT (Alfamino® HMO, Nestlé Health Sciences) to World Health Organization (WHO) growth standards.[31] This single-arm Australian study involved 32 infants (average age: 18.6 weeks), who were followed to 12 months of age. At enrolment, infants in the PLAYTPUS study displayed clinical manifestations of either non-IgE or IgE-mediated CMPA, including eczema/atopic dermatitis (53.1%), urticaria (15.6%), and angioedema (6.3%). The most common symptoms at baseline were persistent crying/irritability (87.5%), frequent regurgitation/vomiting (62.5%), and persistent diarrhoea (59.4%).[31]

Infants in the PLATYPUS study who were fed the HMO-supplemented AAF achieved normal growth, with some evidence of catch-up growth. During the 4-month study period, all anthropometric parameters progressed along the WHO growth reference, with an upward trend from baseline to 4-month follow-up. There was also "prompt" CMPA symptom resolution, noted Nowak-Węgrzyn, with a significant reduction in the frequency of presenting symptoms from enrolment to the 1-month follow-up visit. The HMO-supplemented AAF demonstrated an excellent safety profile, and it was tolerated well by infants with moderate-to-severe CMPA. Only two participants experienced mild gastrointestinal adverse events that were deemed related to the study formula.[31]

In summary, HMOs play an essential role in supporting the developing immune system in infants who are breastfed, and these key nutrients should also be considered in infants who are not breastfed. Development of allergic disease is complex, and several factors contribute, including microbial dysbiosis, immune disturbances, and increased gut permeability, among others. The w-eHF with 2′-FL and LNnT was safe and well tolerated in infants with CMPA, plus it appears to reduce infective morbidity in the first year of life, possibly also reducing oral antibiotic use in these infants. Similarly, infants with moderate to severe CMPA who were fed an AAF with 2′-FL and LNnT achieved normal growth, with some catch-up growth, and the formula was well tolerated in this population. Clearly, these formulae are having a beneficial effect in children with CMPA, Nowak-Węgrzyn concluded.

Evolving Our Understanding of the Impact of 2′-Fucosyllactose and Lacto-N-neotetraose on the Gut Microbiome and Metabolome in Infants with Cow's Milk Protein Allergy

Ralf Heine

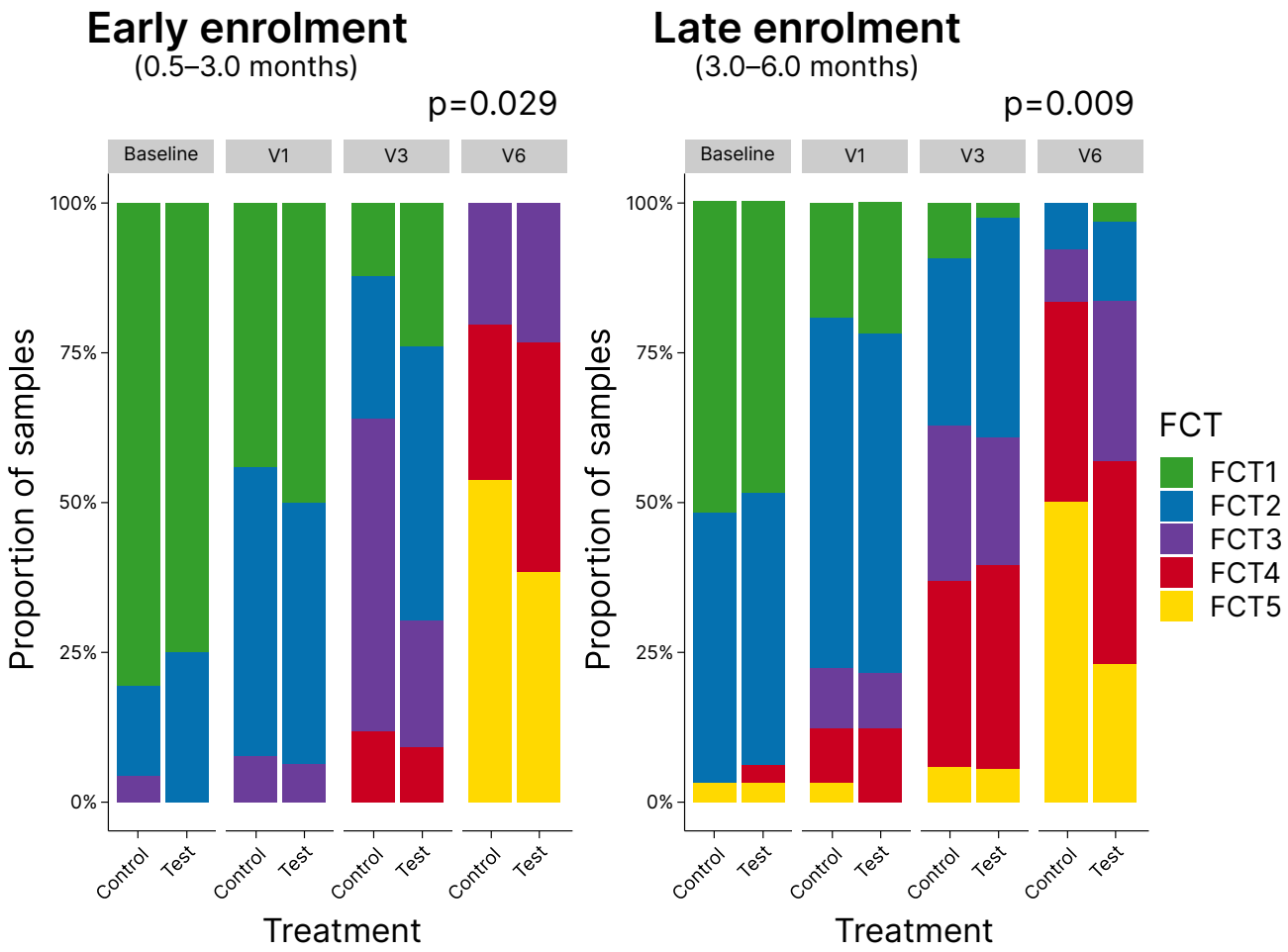
Breast milk is the gold standard for infant nutrition and provides an unparalleled blueprint for formula development. The beneficial effects of breast milk on early immune and gut barrier function are largely driven by HMOs, Heine explained, which are important in the early establishment of an infant-type microbiome. Due to advances in biofermentation technology, it is now possible to produce hypoallergenic infant formula supplemented with the two breast milk identical HMOs, 2′-FL and LNnT, bringing formula composition closer to that of breast milk.[32]

The distinction between infant-type bifidobacteria and the large number of other bifidobacteria is an important one, stressed Heine. Infant-type bifidobacteria are comprised of four species (*Bifidobacterum longum* subspecies *infantis, Bifidobacterium breve, Bifidobacterium bifidum,* and *Bifidobacterum longum* subspecies *longum*), which are specialised in utilising HMOs, and are typical of the early colonisation of the infant microbiome. Lactate and acetate are the main metabolites of this HMO assimilation, and can be cross-fed to other bacteria which co-establish in the infant gut early on. These early coloniser species convert lactate to propionate and acetate to butyrate, the latter having strong tolerance-inducing and immune-modulating properties. Glycosyl hydrolases are bacterial enzymes that break down HMOs. The resulting breakdown products are shared between HMO-utilising bifidobacteria, and may "freeze out" other enteric bacteria via competitive nutrient depletion.[33,34] Aromatic lactic acids produced by infant-type bifidobacteria are a more recent discovery. These compounds, which include indolelactic acid, act as important immune modulators for tolerance development, impacting on both T cell and monocyte responses.[35]

Having outlined the importance of infant-type bifidobacteria in establishing a healthy early-life microbiome, Heine went on to discuss results from the CINNAMON and PLATYPUS studies, assessing the impact of 2′-FL and LNnT on microbiome composition and metabolomic profiles in infants with CMPA (Boulangé et al., unpublished data).[30,31] Stools were collected in the CINNAMON study at baseline, 1 month, 3 months, and 12 months. Shotgun metagenomics analysis was performed in 132 infants with CMPA aged 0.5–6.0 months, together with a faecal community type cluster analysis to assess temporal microbiome changes. A metabolome analysis, encompassing 137 metabolites, was performed in 84 infants.

Results showed preferential enrichment of infant-type bifidobacteria in the early enrolment cohort (aged 0.5–3.0 months at randomisation) of infants fed HMO-supplemented formula. Other bifidobacterial species, such as *B. adolescentis*, were not enhanced, suggesting that HMOs select out the "right bifidobacteria" for the infantile period, Heine explained. Looking at how the microbiome evolved over time, using a transition model of faecal community cluster types, revealed significant differences between test and control groups. In the late enrolment group (3–6 months of age at randomisation), approximately 50% of non-HMO supplemented infants had reached an adult pattern faecal community type 5 (FCT5) by 12 months compared with approximately 25% in the HMO supplemented group (Figure 2). Heine noted that remaining in an earlier, bifidobacteria-enriched microbiome

Figure 2: Transition model of faecal community cluster types in the CINNAMON study.



FCT5: faecal community type 5; V1: 1 month; V3: 3 months; V6: 12 months.

pattern for longer may prolong the window period for early immune modulation, giving infants more time to develop normal immune responses.

From baseline to 1 month, faecal acetate levels increased in the HMO-supplemented group and were reduced in control infants (p=0.09). No significant group differences in acetate signature were observed for subsequent visits but, as Heine explained, fermentation of dietary fibre may obscure the HMO effect once complementary feeding begins. Omics integration was also used to analyse alterations in 16 key metabolites and 17 KEGG orthologues, bacterial enzyme pathways, which were differentially expressed between HMO and non-HMO supplemented groups. Infants fed the HMO-supplemented formula displayed a decrease in conjugated bile acids, with upregulation of bile acid hydrolase activity up to 12 months of age compared with controls. A reduction was also seen in intermediates of branched-chain amino acid (Lys) and aromatic amino acid (Phe, Tyr, Trp) metabolism from 3 months to 12 months of age, indicating downregulation of oxidative protein catabolism via the Ehrlich pathway.

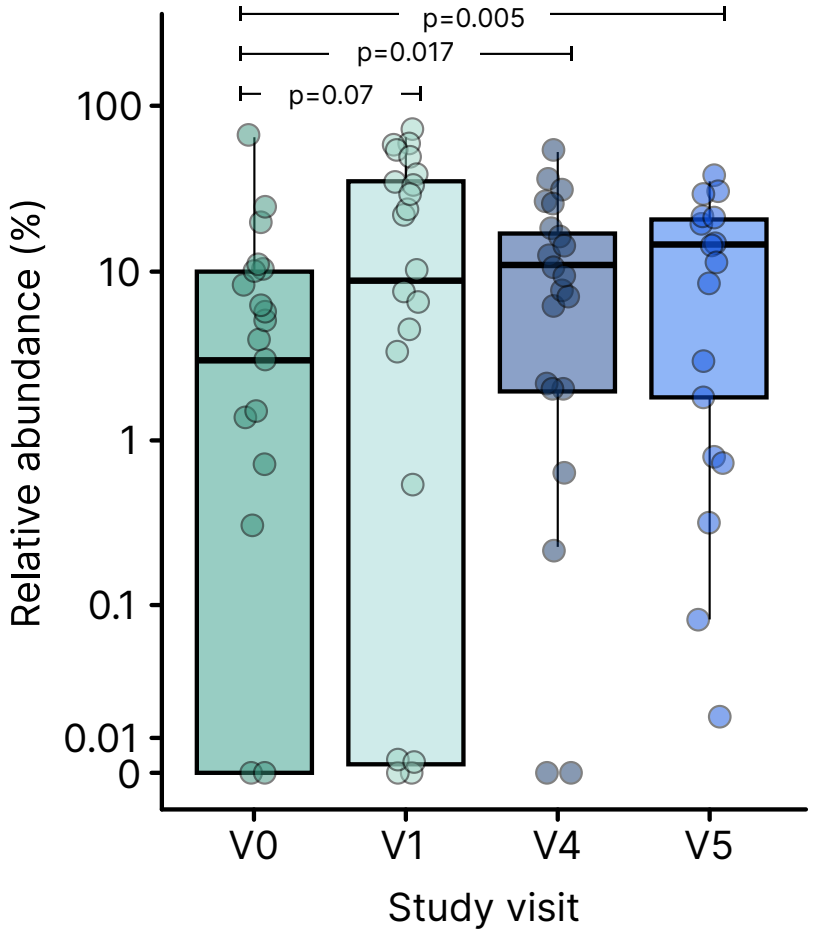
Faecal microbiome analysis was also carried out in the single-arm PLATYPUS study, where samples were available from 29 infants with CMPA at baseline, 1 month, 4 months, and 12 months.[31] At baseline, infants showed a depletion of bifidobacteria. However, by 1 month, the microbial family of *Bifidobacteriaceae* were significantly enriched in response to HMO feeding, which was maintained to 12 months of

age. At the phylum level, actinobacteria, including bifidobacterial, were enriched at 1 month, while abundances of potentially pathogenic proteobacteria were reduced.[31]

Looking specifically at HMO-utilising bacteria, significant enrichment was seen from enrolment in the PLATYPUS study to 12 months of age (Figure 3). Early amplification occurred from baseline to month 1 in the infant-type bifidobacteria, with a further strengthening of the bifidobacteria signal later on. A Taxon Set Enrichment Analysis was also performed on PLATYPUS samples, which revealed increased abundances of *Bifidobacterium* (1 month), *Lachnoclostridium* (Months 1 and 4), and *Bacteroides* (12 months) species, alongside a reduction in levels of *Escherichia coli, Klebsiella, Streptococcus,* and *Rothia* species.[31] So, we can see a picture emerging of increases in early-stage HMO-assimilating bifidobacteria, and a reduction in proteobacteria, leading to partial correction of microbial dysbiosis, Heine explained. The SCFA profile showed that high levels of faecal acetate were maintained throughout the PLATYPUS study period, and butyrate levels significantly increased in the second half of the first year of life, potentially attributable to an HMO effect, with assimilation of acetate by butyrate-producing bacteria such as *Faecalibacterium prausnitzii*.[31]

In summary, these findings show that breast milk-identical HMOs promote an enrichment of the gut microbiome with infant-type bifidobacteria, and reduce the abundance of proteobacteria, suggesting a partial reversal of the microbial

Figure 3: Enrichment of human milk oligosaccharides utilising bifidobacteria in the PLATYPUS study.[31]



V0: baseline; V1: 1 month; V4: 4 months; V5: 12 months.

dysbiosis commonly seen in infants with CMPA. HMO supplementation slowed the premature shift to an adult-type microbiome often seen in infants who are not breastfed, which may prolong the window period for early immune modulation. The metabolomic analysis showed an early increase in faecal acetate, as well as HMO-related changes in bile acid deconjugation and oxidative amino acid catabolism. The full clinical significance remains to be elucidated, and further well-designed studies on the immune-modulating effects of breast milk-identical HMO in infants with CMPA are needed, Heine concluded.

Question and Answer Session

A short question and answer session followed the main symposium, in which panel members were posed questions by the Chair and members of the live audience.

Santos asked at what stage of immune development HMOs are most important, particularly in infants who are not breastfed. Nowak-Węgrzyn replied that formula supplemented with HMOs should be introduced during the first 6 months of life, adding "the earlier, the better."

A member of the audience questioned the rationale for mimicking breast milk with HMO-supplemented formula, given that breastfeeding itself is not protective against food allergy. Heine acknowledged that "it's a complex picture," but stressed that the immunomodulatory effects of breast milk and HMOs on the early life microbiome constitute "the best approach that we currently have" to protect against allergic disease and to avoid prolonged dysbiosis. For CMPA in particular, the aim is for outgrowth, so diagnosis and intervention have to come early, Heine added.

A further audience question asked about the influence of maternal diet on the abundance of protective HMOs in breast milk. Diet plays a role, agreed Heine, as do genetic factors, with approximately 20% of mothers known to be non-secretors of 2'-FL. Different stages of breast milk may also confer different HMO compositions, so trying to mimic all this in formula is a "big ask," Heine acknowledged. However, very encouraging results have been seen in the infection space already, Heine noted, and the "next frontier" will be tolerance development.

Asked about innate and acquired immune mediators in collected stool samples, Heine pointed to aromatic lactic acids, which have emerged as new immune modulatory candidates, and noted that, together with butyrate and other SCFAs, these could act as useful metabolic markers of tolerance development.

Finally, Santos asked about the immune mechanism underlying HMO effects on the reduction of infection and medication use. O'Mahony explained that the epigenetic landscape of immune cells is critical early in life. Factors that promote the "opening up" of the infection countering Th1 immune response and the "closing" of Th2 response to protect against allergy is critical, O'Mahony added, with many factors playing a role, including bifidobacteria and SCFAs.

References

1. Forde B et al. Immunomodulation by foods and microbes: unravelling the molecular tango. Allergy. 2022;77(12):3513-26.
2. Walter J, O'Mahony L. The importance of social networks-an ecological and evolutionary framework to explain the role of microbes in the aetiology of allergy and asthma. Allergy. 2019;74(11):2248-51.
3. Seppo A et al. Human milk oligosaccharides and development of cow's milk allergy in infants. J Allergy Clin Immunol. 2017;139(2):708-11.e5.
4. Miliku K et al. Human milk oligosaccharide profiles and food sensitization among infants in the CHILD Study. Allergy. 2018;73(10):2070-3.
5. Puccio G et al. Effects of infant formula with human milk oligosaccharides on growth and morbidity: a randomized multicenter trial. J Pediatr Gastroenterol Nutr. 2017;64(6):624-31.
6. Lyons A et al. Bacterial strain-specific induction of Foxp3+ T regulatory cells is protective in murine allergy models. Clin Exp Allergy. 2010;40(5):811-9.
7. O'Mahony L et al. Commensal-induced regulatory T cells mediate protection against pathogen-stimulated NF-κB activation. PloS Pathog. 2008;4(8):e1000112.
8. Konieczna P et al. Bifidobacterium infantis 35624 administration induces Foxp3 T regulatory cells in human peripheral blood: potential role for myeloid and plasmacytoid dendritic cells. Gut. 2012;61(3):354-66.

9. Schiavi E et al. The surface-associated exopolysaccharide of Bifidobacterium longum 35624 plays an essential role in dampening host proinflammatory responses and repressing local TH17 responses. Appl Environ Microbiol. 2016;82(24):7185-96.
10. Schiavi E et al. Exopolysaccharide from Bifidobacterium longum subsp. longum 35624™ modulates murine allergic airway responses. Benef Microbes. 2018;9(5):761-73.
11. Groeger D et al. Intranasal Bifidobacterium longum protects against viral-induced lung inflammation and injury in a murine model of lethal influenza infection. EbioMedicine. 2020;60:102981.
12. Martin F-P et al. Host-microbial co-metabolites modulated by human milk oligosaccharides relate to reduced risk of respiratory tract infections. Front Nutr. 2022;9:935711.
13. Venter C et al. The maternal diet index in pregnancy is associated with offspring allergic diseases: the Healthy Start study. Allergy. 2022;77(1):162-72.
14. Roduit C et al. High levels of butyrate and propionate in early life are associated with protection against atopy. Allergy. 2019;74:799-809.
15. Dong P et al. Early-life gut microbiome and cow's milk allergy-a prospective case - control 6-month follow-up study. Saudi J Biol Sci. 2018;25(5):875-80.
16. Luyt D et al. BSACI guideline for the diagnosis and management of cow's milk allergy. Clin Exp Allergy. 2014;44(5):642-72.
17. Crittenden RG et al. Cow's milk allergy: a complex disorder. J Am Coll Nutr. 2005;24(Suppl 6):582S-91S.
18. Francavilla R et al. Effect of lactose on gut microbiota and metabolome of infants with cow's milk allergy. Pediatr Allergy Immunol. 2012;23(5):420-7.
19. Azad M et al. Infant gut microbiota and food sensitization: associations in the first year of life. Clin Exp Allergy. 2015;45(3):632-43.
20. Koopman LP et al. Respiratory infections in infants: interaction of parental allergy, child care, and siblings-- the PIAMA study. Pediatrics. 2001;108(4):943-8.
21. Nowak-Węgrzyn A et al. Confirmed hypoallergenicity of a novel whey-based extensively hydrolyzed infant formula containing two human milk oligosaccharides. Nutrients. 2019;11(7):1447.
22. Jo J et al. Role of cellular immunity in cow's milk allergy: pathogenesis, tolerance induction, and beyond. Mediators Inflamm. 2014;2014:249784.
23. Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology. 2012;22(9):1147-62.
24. Bode L. The functional biology of human milk oligosaccharides. Early Hum Dev. 2015;91(11):619-22.
25. Jalonen T. Identical intestinal permeability changes in children with different clinical manifestations of cow's milk allergy. J Allergy Clin Immunol. 1991;88(5):737-42.
26. Toscana M et al. Role of the human breast milk-associated microbiota on the newborns' immune system: a mini review. Front Microbiol. 2017;8:2100.
27. Thompson-Chagoyan OC et al. Faecal microbiota and short-chain fatty acid levels in faeces from infants with cow's milk protein allergy. Int Arch Allergy Immunol. 2011;156(3):325-32.
28. West C et al. The gut microbiota and its role in the development of allergic disease: a wider perspective. Clin Exp Allergy. 2015;45(1):43-53.
29. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant fomulas. Pediatrics. 2000;106(2 Pt 1):346-9.
30. Vandenplas Y et al. Effects of an extensively hydrolyzed formula supplemented with two human milk oligosaccharides on growth, tolerability, safety and infection risk in infants with cow's milk protein allergy: a randomized, multi-center trial. Nutrients. 2022;14(3):530.
31. Gold MS et al. Effects of an amino acid-based formula supplemented with two human milk oligosaccharides on growth, tolerability, safety, and gut microbiome in infants with cow's milk protein allergy. Nutrients. 2022;14(11):2297.
32. Vandenplas Y et al. Human milk oligosaccharides: 2'-Fucosyllactose (2'-FL) and Lacto-N-Neotetraose (LNnT) in infant formula. Nutrients. 2018;10(9):1161.
33. Milani C et al. The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. Microbiol Mol Biol Rev. 2017;81(4):e00036-17.
34. Gotoh A et al. Sharing of human milk oligosaccharides degradants within bifidobacterial communities in faecal cultures supplemented with Bifidobacterium bifidum. Sci Rep. 2018;8(1):13958.
35. Laursen MF et al. Bifidobacterium species associated with breastfeeding produce aromatic lactic acids in the infant gut. Nat Microbiol. 2021;6:1367-82.

Abstract Review

Featuring fascinating research from the European Association of Allergy and Clinical Immunology (EAACI) 2023 Congress, focusing on the impacts of cultivation conditions on the expression of airborne allergens.

The Impact of Different Cultivation Conditions on the Expression of *Alternaria alternata* Allergens

Authors: Sandra Pfeiffer,[1] Margarete Focke-Tejkl,[2,3] Katja Sterflinger,[4] Ines Swoboda[1]

1. The Molecular Biotechnology Section, FH Campus Wien, University of Applied Sciences, Vienna, Austria
2. Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology, and Immunology, Medical University of Vienna, Austria
3. Working Group Danube Allergy Research Cluster (ARC), Karl Landsteiner University of Health Sciences, Krems, Austria
4. Department of Natural Sciences and Technology in the Arts, Academy of Fine Arts Vienna, Austria

*Correspondence to ines.swoboda@fh-campuswien.ac.at

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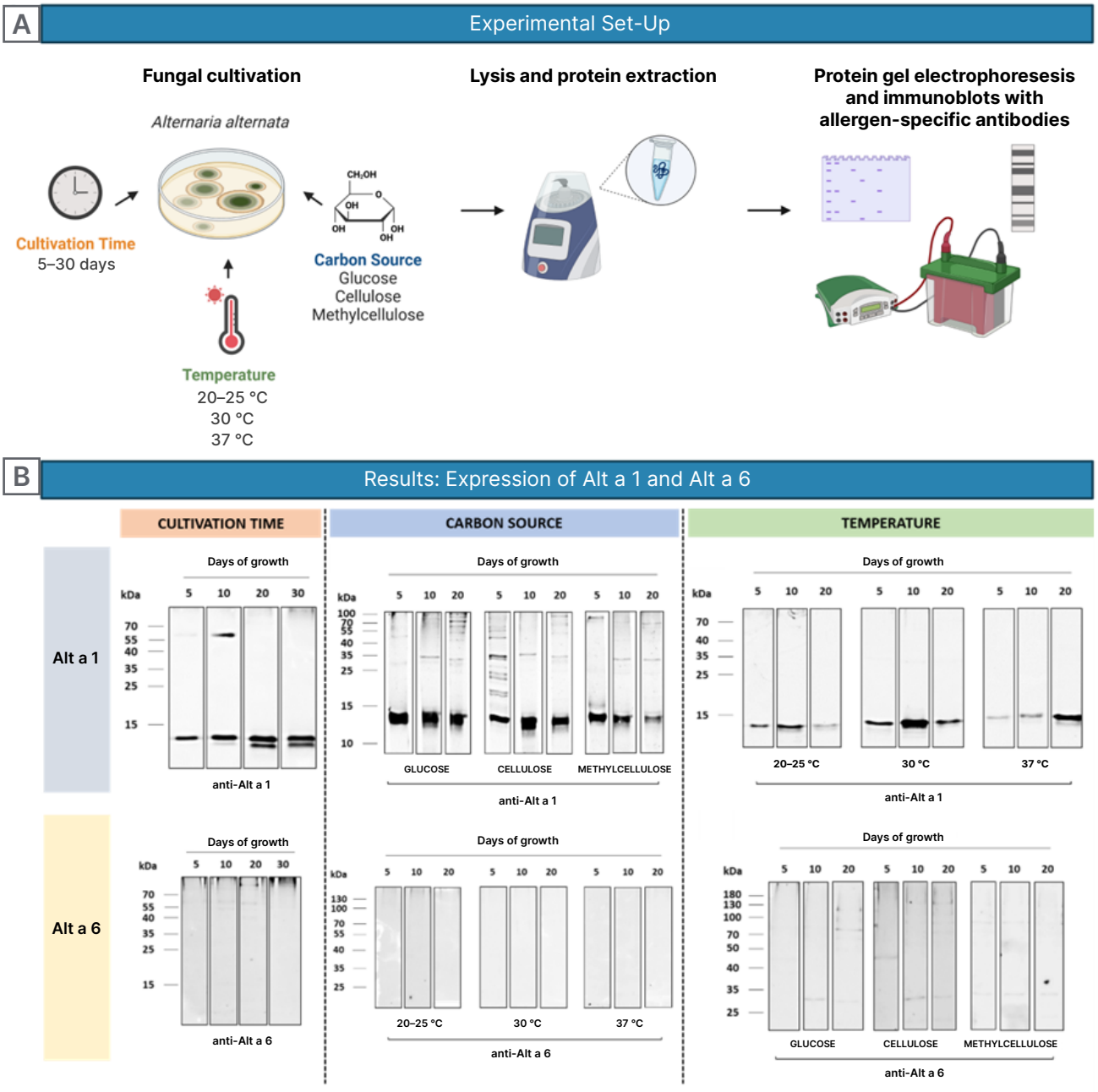
BACKGROUND AND AIMS

Alternaria alternata is one of the most potent sources of airborne allergens.[1,2] However, the diagnosis of *A. alternata* sensitisation is hampered by the poor quality of allergy test solutions.[3] Cultivation conditions can have a major impact on the allergens present in mould extracts.[3-5] The majority of previous studies have mainly focused on the effect of growth parameters on the expression of single allergens, without analysing the occurrence of other allergens.[6,7] Multiple *A. alternata* allergens have already been identified and characterised.[1,8] Two molecules, the major allergen Alt a 1 (15 kDa) and the cross-reactive allergen Alt a 6 (47 kDa), are the species' most relevant allergens.[1,8] The aim of this study was to investigate the impact of different cultivation conditions on the expression of these two allergens.

MATERIALS AND METHODS

To analyse the effect of environmental conditions on fungal allergen expression (Figure 1A), clones of *A. alternata* were cultivated in the presence of different carbon sources (i.e., glucose, cellulose, and methylcellulose), or at different temperatures (i.e., 20–25 °C, 30 °C, 37 °C). Then, protein extracts were prepared from the fungal material (mycelium and spores), which were harvested after different days of growth. To detect the expression of the allergens Alt a 1 and Alt a 6, Western blots with allergen-specific antibodies were carried out.

Figure 1: Analysis of the impact of different cultivation conditions on the expression of *Alternaria alternata* allergens.



A) Experimental set-up for the analysis of the impact of different cultivation conditions on the expression of the *Alternaria alternata* allergens Alt a 1 and Alt a 6. **B)** Expression of Alt a 1 and Alt a 6 in *A. alternata* grown under different conditions (cultivation time, carbon source, temperature), shown by anti-Alt a 1 and anti-Alt a 6 immunoblots.

rAlt a 1: recombinant Alt a 1; rAlt a 6: recombinant Alt a 6.

RESULTS

Western blots performed with antibodies directed against Alt a 1 and Alt a 6 showed that the expression of the fungal allergens is highly molecule-dependent. The carbon source, cultivation temperature, and growth time did not have a major impact on the expression of Alt a 1, as fungal allergen extracts containing the allergen could be easily produced from fungi grown under various conditions (Figure 1B). For example, Alt a 1 could still be

extracted from very small amounts of fungal biomass that was harvested after 5–20 days of growth at 37 °C. Moreover, results of anti-recombinant Alt a 1 immunoblots revealed that the growth on glucose, an easily accessible substrate, compared with the growth on more complex carbon sources (i.e., cellulose, methylcellulose), did not have a major impact on the expression of Alt a 1. In contrast, Alt a 6 could not be detected in protein extracts prepared from *A. alternata* grown under any condition (Figure 1B). These results demonstrate the difficulty in producing reliable allergen extracts containing fungal enolase.

CONCLUSION

Taking *A. alternata* as an example, the authors' data reveal that even though certain cultivation conditions might lead to strong expression of one allergen, the same conditions might not be optimal for the expression of another allergen. This emphasises the necessity of determining the optimal cultivation and extraction conditions for each allergen separately. Information obtained in this study will help to optimise fungal cultivation to produce highly potent diagnostic fungal extracts, and therefore to improve allergy diagnosis. In the future, it will be of interest to also investigate the effect of further cultivation conditions on the expression of *A. alternata* allergens, to include additional allergens in investigations and, of course, to extend the analyses to further fungal species.

References

1. Simon-Nobbe B et al. The spectrum of fungal allergy. Int Arch Allergy Immunol. 2008;145(1):58-86.
2. Gabriel MF et al. Alternaria alternata allergens: markers of exposure, phylogeny and risk of fungi-induced respiratory allergy. Environ Int. 2016;89-90:71-80.
3. Twaroch TE et al. Mold allergens in respiratory allergy: from structure to therapy. Allergy Asthma Immunol Res. 2015;7(3):205-20.
4. Twaroch T et al. Specific antibodies for the detection of alternaria allergens and the identification of cross-reactive antigens in other fungi. Int Arch Allergy Immunol. 2016;170(4):269-78.
5. Schmid-Grendelmeier P, Crameri R. Recombinant allergens for skin testing. Int Arch Allergy Immunol. 2001;125(2):96-111.
6. Arruda LK et al. Selective expression of a major allergen and cytotoxin, Asp f I, in Aspergillus fumigatus. Implications for the immunopathogenesis of Aspergillus-related diseases. J Immunology. 1992;149(10):3354-9.
7. Ibarrola I et al. Production profile of the major allergen Alt a 1 in Alternaria alternata cultures. Ann Allergy Asthma Immunol. 2004;93(6):589-93.
8. Postigo I et al. Diagnostic value of Alt a 1, fungal enolase and manganese-dependent superoxide dismutase in the component-resolved diagnosis of allergy to pleosporaceae. Clin Exp Allergy. 2011;41(3):443-51.

Abstract Highlights

The following highlights spotlight selected abstracts presented at the 2023 European Academy of Allergy and Clinical Immunology (EAACI) Congress. They cover fascinating and timely topics, including the effect of infantile atopic dermatitis on maternal bonding, patient burden in hereditary angioedema, and the use of specific interleukins to reduce symptoms of allergic rhinitis.

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What Factors Contribute to FPIES Reactions at Oral Food Challenge?

A MULTICENTRE, prospective, observational study was led by researchers at Imperial College London, UK, to assess potential factors associated with reaction severity in food protein-induced enterocolitis syndrome (FPIES). The study aimed to outline the clinical symptoms and routinely available blood parameters in children experiencing reactions. There is currently limited knowledge surrounding the clinical and immunological symptoms experienced by patients with FPIES, and with a lack of diagnostic and prognostic biomarkers, oral food challenge (OFC) remains the current gold standard in its diagnosis.

The researchers conducted the study in children aged 0–18 years in 15 tertiary allergy clinics in France and Spain. The participants had been diagnosed with acute FPIES and were undergoing follow-up OFC to identify the cause of their reaction. OFCs were performed on either single day protocols with incremental doses, or 2-day protocols with a single dose of 25% of an age-appropriate portion on Day 1, with a reminder on Day 2.

Outcomes were interpreted using the FPIES consensus criteria, published in 2017, and children with a positive outcome were included. The researchers logged the participants' clinical characteristics and blood parameters at baseline, at the onset of reaction, and 4 hours later. Regression analyses were conducted for potential predictors of severe OFC reactions.

"The researchers conducted the study in children aged 0–18 years in 15 tertiary allergy clinics in France and Spain."

This study found 81 children with positive OFC. Of this cohort 87.6% followed a 1-day protocol, and 70% had experienced previous severe reactions. Reaction severity was reported as mild in 11% of participants, moderate in 61%, and severe in 28%, with an increase in neutrophils and a reduction in eosinophils and lymphocytes remarked at OFC ($p<0.05$). Analyses showed that a 2-day OFC protocol correlated with reduced odds of severe reaction, and other factors including sex, age, and culprit foods were not associated with severity.

Overall, this study suggested that the 2-day protocol may be associated with less severity at FPIES OFC. The researchers highlighted the need for the development of safer FPIES diagnostics, given the high rates of moderate-to-severe reactions observed in this study.

Clinical Outcomes Following Allergen Exposure Chambers

ALLERGEN exposure chamber (AEC) is a diagnostic tool that permits exposure to allergenic and non-allergenic airborne particles. Used for diagnosing and for monitoring the effects of treatment, AECs provide a stable concentration of particles under controlled conditions, independent of external factors. The research team therefore sought to validate AEC-derived clinical outcomes of house dust mite (HDM) allergy immunotherapy (AIT).

Fifty patients with symptoms of HDM-triggered allergic rhinoconjunctivitis received skin prick tests, serum specific IgE, and basophil activation test to confirm the diagnosis. Allergy symptoms were then assessed using Combined Symptom and Medication Score (CSMS). AEC was used to assess patients both before and 12 months after treatment with subcutaneous HDM AIT. Standardised and lyophilised allergen extract particles were injected into the AEC through a computer controlled feeder during exposure. An optimal concentration of 5000 μ/m^3 of purified bodies of *Dermatophagoides pteronyssinus* was utilised for a challenge duration of 120 minutes. AIT efficacy was assessed using the Total Nasal Symptom Score (TNSS), Visual Analogue Scale (VAS), and objective parameters, such as peak nasal inspiratory flow, nasal secretion weight, and acoustic rhinometry.

Analysis suggested that constant environment conditions, including temperature, humidity, and carbon dioxide concentrations, were maintained for all challenges. Most importantly, TNSS was significantly reduced after one year of AIT ($p<0.005$) and a high reduction of nasal symptoms, such as peak nasal inspiratory flow and nasal secretion weight, were observed after a year of AIT ($p<0.05$). However, no statistically significant changes to acoustic rhinometry was seen following AIT. Finally, a strong correlation was observed between CSMS in field measured before treatment and nasal symptoms measured in AEC ($p<0.05$), using nasal secretion ($r=0.77$; $r=0.99$), peak nasal inspiratory flow ($r=0.80$; $r=0.75$), and VAS ($r=0.93$; $r=0.81$) before and after AIT, respectively.

Overall, the AEC is an effective, safe, and reproductible method for assessing HDM AIT outcomes in patients with allergic rhinoconjunctivitis. Future research and clinical practice would benefit from further validation of clinical endpoints using immunological biomarkers. ●

"AEC was used to assess patients both before and 12 months after treatment with subcutaneous HDM AIT."

Infantile Atopic Dermatitis and Maternal-Infant Bonding: A Mixed Methods Study

RESEARCH presented at the EAACI 2023 Congress explored infantile atopic dermatitis, a common, chronic skin condition characterised by the presence of dry, itchy, and inflamed skin. Previous studies and literature have delved into the impact of this condition on children and caregivers' quality of life; however, until recently, there has been little understanding of, or research dedicated to, the impact of the condition on the relationship between mothers and infants. This mixed-methods study aimed to assess the association between infantile atopic dermatitis and the maternal–infant bond.

The study used adjusted models with scores on the impaired bonding, pathological anger, and incipient abuse subscales, which did not significantly differ between case and controls. Further analysis demonstrated that mothers of infants with atopic dermatitis reported lower levels of infant-directed anxiety (β=-1.06; p=0.04). However, qualitative findings supported the idea that regular caregiving required for infants with infantile atopic dermatitis may strengthen the bond between some mothers and infants. The study participants had an average age of 30.80±4.36 years, and an average infant age of 7.60±4.20 months.

The researchers concluded that the mother–infant bond does not appear to be negatively impacted by the presence of infantile atopic dermatitis. On the contrary, analysis suggested that the requirement for the provision of routine care for infants with atopic dermatitis instead strengthens the bond between mothers and their infants. ●

"There has been little understanding of, or research dedicated to, the impact of the condition on the relationship between mothers and infants."

Symptom and Quality of Life Burden in Patients with Indolent Systemic Mastocytosis

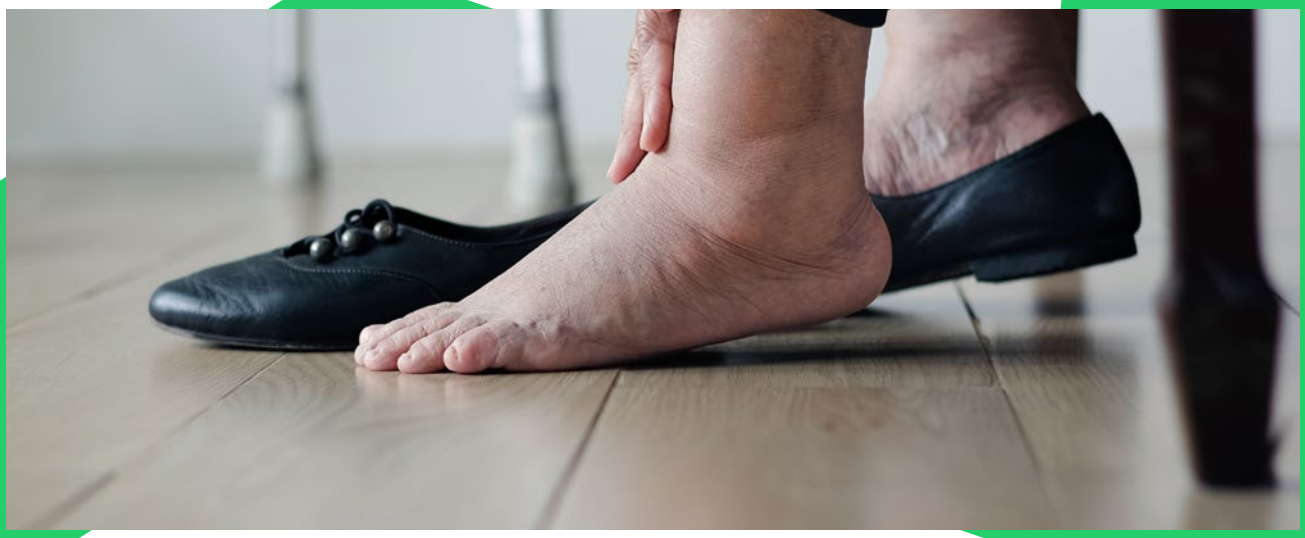
AT THE EAACI Congress 2023, Frank Siebenhaar, Charité – Universitätsmedizin Berlin, Germany, presented data from a registrational, randomised, double-blinded, placebo-controlled study. The study included patients with moderate-to-severe indolent systemic mastocytosis (ISM) with inadequately managed symptoms, despite receiving optimised treatment with two or more anti-mediator drugs.

The symptom burden was evaluated at baseline prior to the start of the study, using the ISM-symptom assessment form, which calculated the total symptom score (TSS) ranging from 0–110. The TSS was established based on a 14-day average of patient-reported severity for 11 ISM symptoms, with the scores ranging from 0 (referring to no symptoms) to 10 (indicating the worst imaginable symptoms). The patients were required to have a TSS ≥28 at screening to be eligible for inclusion. Various measures, including the 12-Item Short-Form Health Survey (SF-12), European Quality of Life 5 Dimensions (EQ-5D-5L), Mastocytosis Quality of Life Questionnaire (MC-QoL), and Patient Global Impression of Severity (PGIS), were utilised to assess patient health status and quality of life.

Prior to study initiation, enrolled patients (n=212) reported severe ISM symptoms. Multiple symptom-directed therapies were utilised, including H1 and H2 antihistamines (98.1% and 66.0%, respectively), and leukotriene receptor antagonists (34.9%); however, the mean TSS was 50.9. In comparison to general population norms, other chronic conditions, and cancers, the enrolled patients had lower scores, indicating worse physical and mental health. Notably, the mean physical component score of the SF-12 was 33.9, while the mean mental component score was 40.7. Additionally, the patients exhibited lower mean scores on the EQ-5D-5L index (0.62), compared to the general population (0.85).

"The symptom burden was evaluated at baseline prior to the start of the study, using the ISM-symptom assessment form."

The patients reported moderate disease severity based on MC-QoL, with a mean score of 57.5 on a range of 0–100, where ≥40 indicates moderate severity. When assessing symptom severity, patients rated their symptoms as very severe (22%), severe (33%), or moderate (36%) using the PGIS. The findings indicate that a substantial existing disease burden, and highlight the unmet needs of individuals with moderate-to-severe ISM.



Quality of Life and Patient Burden of Hereditary Angioedema in Resource-Limited Regions

HEREDITARY angioedema (HAE) data are prevalent across Europe and North America, but limited in other regions around the world, where healthcare systems are less well-developed, and access to treatments recommended in guidelines are limited. HAE, which causes sudden, painful, and recurrent swelling in patients, is a rare disorder that can be life-threatening.

Lead study author Rand Arnaout, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, embarked on this research topic with colleagues from Mexico, Singapore, and South Korea. The team carried out a cross-sectional, non-interventional, Internet-based survey in a patient cohort who had been diagnosed with HAE by a physician. Data was taken from four countries (Türkiye, Mexico, South Korea, and Saudi Arabia), with the starting point of 1st July 2022. Patients needed to be ≥18 years; have had ≥1 attack of HAE, or early warning symptoms of an attack within the last year; and have received medication for HAE within the last 2 years.

Researchers collected outcomes, patient-reported burden, and clinical characteristics data. They used the following outcome measures: the Angioedema Quality of Life (AE-QoL), the Hospital Anxiety and Depression Scale (HADS), and the Angioedema Control Test (AECT). The interim analysis ran until 31st January 2023.

In total, 116 patients were included (87 from Türkiye; zero from Mexico; 27 from South Korea; two from Saudi Arabia), with a mean age of 41.1 years. Of these, 59% were female, and 79% had Type I or II HAE. Median HAE onset age was 14.1 years, and diagnosis age was 27.1 years. Over the previous 12 months, 55% of these patients had >2 attacks per month on average, with 3% reporting ongoing attacks. These attacks were reported as severe or very severe in 61 out of 110 patients, 33% of whom were receiving long-term prophylaxis (most common: danazol [76%] and tranexamic acid [10%]), and 78% of whom were receiving on-demand treatment. Three-quarters of patients had AECT scores <10; the majority had AE-QoL scores ≥50; and 45% and 25% of patients had moderate-to-severe anxiety and depression, respectively, using the HADS score.

"Researchers collected outcomes, patient-reported burden, and clinical characteristics data."

Researchers concluded that in resource-limited regions, patients with HAE had a >10-year delay from onset to diagnosis, and also experienced severe attacks frequently. There was also found to be a substantial disease burden in this cohort. ●

Decreasing Allergic Rhinitis Symptoms with Low-Dose IL-2

LOW-DOSE IL-2 can decrease allergic rhinitis symptoms in patients, according to research presented at the EAACI Congress 2023. Researchers based in France performed a randomised, double-blind, placebo-controlled, parallel-group Phase IIA study to evaluate the efficacy of low-dose IL-2 on nasal response during birch allergen exposure.

A total of 24 patients, with a specific IgE to birch and a positive skin prick test, took part in the study. Their exposure to birch allergen was in an environmental exposure chamber, which the researchers deemed a good model to evaluate the efficacy of drugs on rhinitis symptoms in patients with allergies.

Firstly, patients were exposed to 25 ng/m^3 of Bet v I allergen to determine nasal response, and for the researchers to pick patients who had a positive nasal response, which was defined as a Total Nasal Symptom Score (TNSS) of ≥5 compared with baseline. The researchers also assessed rhinitis visual analogue scale (VAS) and asthma response, defined as a drop of ≥20 forced expiratory volume in 1 second.

After being randomised, the patients were either given a placebo or low-dose IL-2 (1 million IU/day) for 5 consecutive days. This was followed by a maintenance period, which either consisted of an injection of placebo or low-dose IL-2 for 4 weeks (from Day 15 to Day 36). Allergen exposure tests were performed after treatment on Days 8 and 40.

The results showed a decrease in TNSS in the IL-2 group, with an area under the curve of 8.03 at Day 40, compared with 3.27 for placebo. The area under the curve for rhinitis VAS was -32.31% compared with placebo. Patients on low-dose IL-2 also had a 1.5-fold increase in T regulatory cells, which play an important part in sustaining immune tolerance to allergens, and the researchers observed significant changes in spirometry.

In conclusion, low-dose IL-2 can decrease rhinitis symptoms, while increasing regulator T cells in an environmental exposure chamber. ●

"A total of 24 patients, with a specific IgE to birch and a positive skin prick test, took part in the study."

Do Comorbidities and Aeroallergen Sensitisation Affect Asthma Severity in Children?

ALLERGIC rhinitis and weed sensitisation have been identified as independent risk factors for low asthma severity in paediatric patients in a retrospective cohort study presented at EAACI 2023. The study aimed to investigate how comorbidities and aeroallergen sensitisation affect asthma severity in children.

Researchers collected data from a prospectively collected registry of 976 paediatric patients with asthma, who were enrolled in the National Pediatric Asthma Cohort Study between July 2016–January 2019. The team investigated baseline characteristics of all participants, including comorbidities, pulmonary function tests, and aeroallergen sensitisation with T helper 2 markers. Participants were classified into four groups. Group A included patients without comorbidities; Group B patients with atopic dermatitis (AD) only; Group C those with allergic rhinitis (AR) only; and Group D with AD and AR.

The team noted differences in asthma severity, initial fractional exhaled nitric oxide, and degree of sensitisation by aeroallergen group according to the comorbidities. Those in the AD only group had the highest proportion of moderate-to-severe asthma, while those in the AR only group had the lowest. Regarding fractional exhaled nitric oxide, this was lowest in the group without comorbidity, followed by the AD only group, and finally the group with both AD and AR. The AR group had high sum of skin prick tests wheels by each aeroallergen sensitisation group, except animal dander. Furthermore, total IgE and sum of skin prick tests wheels of weed were identified as predictors of AR and AD comorbidities in children with asthma. Multivariate logistic regression analysis showed that weed sensitisation and AR were negative risk factors for moderate-to-severe asthma.

"The team investigated baseline characteristics of all participants, including comorbidities, pulmonary function tests, and aeroallergen sensitisation with T helper 2 markers. "

The team concluded that AR and weed sensitisation were independent risk factors for low asthma severity in paediatric patients. The authors highlighted that this shows the need for reinterpretation of previous findings, which showed that most comorbidities associated with asthma adversely affect severity and prognosis. More studies, on a larger scale, are needed to further examine the definition of airway hyperresponsiveness, aeroallergen sensitisation, and the diagnosis of asthma according to comorbidities.

Allergic Rhinitis: Does Intranasal Phototherapy Improve Nasal Symptom Scores?

TOTAL nasal symptom score (TNSS) is a validated symptom-rating questionnaire used to quantify allergic rhinitis (AR) symptoms. Despite standard approaches, some patients have persistent symptoms. Intranasal phototherapy is a type of ultraviolet light therapy used alongside standard medical therapy to help treat AR.

To determine whether intranasal phototherapy improves AR symptoms in adolescent patients who failed to respond to standard treatment, a group of researchers from Birmingham, UK, conducted a retrospective analysis of data from all adolescent patients who underwent intranasal phototherapy for AR between July 2018–July 2022. In total, the analysis included 32 patients with AR. The mean age was 13.5 years and 26 were male. Most patients had a diagnosis of perennial rhinitis (81.8%).

The study revealed that intranasal phototherapy resulted in improved TNSS questionnaire results. The average pre-treatment TNSS was 8.7 (95% confidence interval [CI]: 7.5–9.9; range: 3.0–14.0), which reduced to 4.0 (95% CI: 2.8–5.2; range: 0.0–13.0), following intranasal phototherapy. The average difference pre- and post-treatment with intranasal phototherapy was 4.7 (95% CI: 3.3–6.0), translating to an overall TNSS improvement of 54%.

"The study revealed that intranasal phototherapy resulted in improved TNSS questionnaire results."

Whilst this study was performed in a small sample, and relied on self-reporting of TNSS questionnaires, the authors concluded that intranasal phototherapy improves AR symptoms, demonstrated by an improvement in TNSS. Research in larger cohorts, as well as studies to compare symptom responses to oral medications, including antihistamine and steroid treatment versus intranasal phototherapy, could be a potential focus for the future.

Reducing Inflammation in Chronic Rhinosinusitis with Nasal Polyps

WHILE exerting different effects on local immune pathways, mepolizumab, benralizumab, omalizumab, and dupilumab downregulated proteins and genes related to eosinophilic inflammation in patients with chronic rhinosinusitis with nasal polyps (CRSwNP).

Type 2 nasal and sinus mucosa inflammation is common in patients with CRSwNP. It is characterised by high levels of IgE, IL-5, and eosinophilic cationic protein, as well as tissue eosinophilia. Up to 65% of these patients have comorbid asthma, and treatment involves drugs that treat severe, uncontrolled asthma. As knowledge of the local working mechanisms of these biologics is limited, Sharon Van Nevel, Upper Airways Research Laboratory, Ghent, Belgium, and colleagues studied how difficult biologicals modulate Type 2 airway inflammation.

Nasal polyp tissue was taken from patients before and during treatment, and immunohistochemistry stainings and protein measurements were performed. Patients were diagnosed with Type 2-high CRSwNP before treatment. Pre- and post-treatment samples from the same patients were then RNA-sequenced in bulk, with DESeq 2 (R4.2.0 [Bioconductor]) used to identify differentially expressed genes.

Patients were treated with mepolizumab (anti-IL-5), benralizumab (anti-IL-5-receptor), and omalizumab (anti-IgE), where eosinophils withdrew from the tissue and neutrophils were attracted locally. This was not present in dupilumab (anti-IL-4/13-receptor) treatment. Patients treated with mepolizumab showed a decrease in eosinophil markers, T cells, and apoptosis; however, there was an increase in mucus-related and neutrophilic genes. A similar downregulation of eosinophil-associated genes and upregulation of neutrophilic markers was seen with omalizumab treatment. However, this was not the case with dupilumab, where there were lower genes associated with eosinophils, and no upregulation of genes associated with neutrophils.

The researchers concluded that mepolizumab, benralizumab, omalizumab, and dupilumab resulted in the downregulation of eosinophilic inflammation-related proteins and genes. The upregulation seen during treatment with mepolizumab, benralizumab, and omalizumab suggests that there is a switch from eosinophilic to neutrophilic inflammation. However, this was not observed with dupilumab, which could explain the higher response rate in patients with CRSwNP. ●

"Nasal polyp tissue was taken from patients before and during treatment."

Are IgE Food Allergens Associated with Cardiovascular Disease?

SENSITISATION to food allergens and cardiovascular mortality risk were evaluated by a team of researchers from multiple centres across the USA. The team reviewed data from the cross-sectional National Health and Examination Survey (NHANES) and the Multi-Ethnic Study of Atherosclerosis (MESA) longitudinal cohort, both of which gathered detailed dietary information and food specific IgE data.

"Sensitisation to CM only was associated with significantly higher risk of cardiovascular mortality."

The NHANES survey included 4,996 adults, and included total and specific IgE to cow's mik (CM), egg, peanut, and shrimp, measured using ImmunoCAP™ (Thermo Fisher Scientific, Waltham, Massachusetts, USA), as well as linked mortality data up to 2019. MESA included adult patients with no clinical diagnosis of cardiovascular disease between 2000–2002. In a subset of this cohort, specific IgE for CM, alpha-gal syndrome, and peanut were measured using ImmunoCAP.

Cox proportional hazard models, adjusted for age, asthma, education, race/ethnicity, sex, and smoking history, were used to assess food sensitisation and cardiovascular death. Food sensitisation was defined as IgE >0.35 kU_A/L.

Results showed that 15% patients in the NHANES study were sensitised to at least one food, with 4%, 3%, 7%, and 6% being sensitised to CM, egg, peanut, and shrimp, respectively. Of the 960 patients in the MESA cohort, 4% were sensitised to CM, 0.8% to alpha-gal, and 7% to peanut. There were 264 cardiovascular deaths in the NHANES study, and 69 in the MESA cohort.

Sensitisation to CM only was associated with significantly higher risk of cardiovascular mortality in both studies (hazard ratio [HR]: 2.1; 95% confidence interval [CI]: 1.1–4.0; p=0.026 in the NHANES study, and HR: 3.8; 95% CI: 1.6–9.1; p=0.003 in the MESA cohort). In the MESA cohort, CM sensitisation was highly associated with non-atherosclerotic causes of cardiovascular mortality (HR:10.8; 95% CI: 3.5–32.4; p<0.001) and heart failure events, but not death due to atherosclerotic cardiovascular disease or myocardial infarction. Furthermore, an analysis limited to those who consumed a given food allergen in the NHANES study, unmasked shrimp sensitisation as a significant risk factor for cardiovascular mortality (HR: 2.9; 95% CI: 1.1–7.7; p=0.03).

From these findings, the authors concluded that sensitisation to food was associated with increased cardiovascular mortality, especially CM sensitisation. They highlighted that this association seems to be strengthened in regular consumers, which could indicate that even in the absence of symptoms, food sensitisation may not be benign.

Congress Interviews

Stefano del Giacco
Department of Experimental and Clinical Medicine, University of Cagliari, Italy; and European Academy of Allergy & Immunology (EAACI) President of Congresses

Mohamed Shamji
Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College London, UK; and EAACI Vice-President of Congresses

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EMJ had the pleasure of interviewing Stefano del Giacco and Mohamed Shamji at EAACI 2023 in Hamburg, Germany. The experts shared insights into this year's congress in this exclusive roundtable interview.

Q1 How is the European Academy of Allergy & Immunology (EAACI) supporting physicians and researchers with the best practices and tools to enable standard, high-quality care in allergy and asthma?

S: This is part of the EAACI mission; our guidelines and position papers are used daily by researchers, clinicians, and scientists around the world. We are striving to continuously update our papers and guidelines, and to work collaboratively with our sister societies to align guidelines.

M: In addition to the points Stefano has made, I would like to underline the success of the EAACI Congress 2023, here in Hamburg, Germany. We have over 7,000 attendants joining us physically, as well as many more who are participating virtually, and the majority of those participants are clinicians. This means we are reaching out to those allergy and immunology clinicians for the purposes of both education and best practices. This education is presented in the form of plenaries, symposia, lectures, and guidelines, and allows us to communicate all the relevant activities that are happening within EAACI. However, most important is the variety of attendees; we have scientists, clinicians, and allied health professionals, to name a few. We are bringing these people together and providing a translational approach from bench to bedside, with the aim of reaching out to our patients. The motto for the congress is 'precision medicine to personalised medical approaches in allergy and asthma', and we truly feel that we cover this.

"We are bringing these people together and providing a translational approach from bench to bedside."

Q2 Are there any significant changes that you witnessed during your tenure as the President (del Giacco) and Vice-President (Shamji) of EAACI?

S: We have both been in our roles for 1 year now. However, as with previous EAACI leaders, we have brought our own touch to the academy and the congress. We had the heavy responsibility of starting again after the COVID-19 pandemic. Last year, we had a fantastic congress in Prague, Czechia; however, this was a trial run to allow us to come back full throttle this time around. This was mine and Shamji's task, and I am proud to say that this is something we feel we have fully accomplished.

Another priority for us is to bring a touch of innovation in every field, from technology to science to general topics. Additionally, to be open in a wider perspective to the wider community of science, from students to keynote speakers, and also to the lay public.

> **"Another priority for us is to bring a touch of innovation in every field."**

M: I really feel the same! Coming out of COVID-19 has been one of the defining aspects of our presidency so far. The challenges this has posed in previous years with online and hybrid congresses have mirrored the outside world, with the rise of telemedicine for patients, and the technological advancements that have followed, such as artificial intelligence (AI) and machine learning. We are now in the position to implement the advancements made during the pandemic in an increasingly efficient way as we are now meeting face-to-face, networking, sharing ideas, and following them through to completion.

I am proud to say that we have truly taken lessons from the pandemic and applied them to our actions today. We have had fantastic support from within the society, which has allowed us to be where we are today.

Q3 What are the most exciting changes that have been made to this year's EAACI programme, compared to the previous year's congress?

M: Last year, we focused on technology, with AI, telemedicine, molecular allergology, and translational medicine, which has always been at the heart of the EAACI mission. The key element for us this year is to take what we have learnt, and really focus on addressing the unmet needs both in patients and in the medical community in allergy and asthma. Additionally, we have moved the focus from precision medicine to personalised medicine. Precision medicine is incredibly important, and personalised medicine is even more essential, as we know the heterogeneity of patient responses when they receive treatment. With the novel tools that have been developed, we are now able to stratify patients, and really target patients with specific personalised treatments that we know they will

benefit from. Additionally, we are seeing many more biomarker-driven approaches to treatment alongside novel therapeutic development.

S: I fully agree. I would also like to highlight our key message, which is that we try to make real what has, for a long time, been just a discussion, such as AI, machine learning, precision medicine, and personalised treatments. We have tried to design a congress that brings together theory, but with a particular focus on shifting and translating theory into practice for our doctors and scientists. I strongly feel that this is one of the greatest achievements of the EAACI Congress 2023.

Q4 Could you highlight any particular sessions or presentations that you highly recommend attending this year?

S: I would like to be a little original and recommend the keynote lecture, because it was very novel and different, focusing on observation, science, and medicine, and it raised important considerations for medical practice. The keynote focused on the importance of observing, not just seeing patients, which I feel is a general message to the medical community at large. When you start truly observing patients, you find new solutions. For example, with the pandemic, we saw the development of the COVID-19 vaccine and many new drugs in a very short period. Usually it takes a much longer time to find solutions to these problems.

I would also recommend keeping an eye out for sessions on One Health, as it encompasses all of planetary health, including food, climate, and a number of other essential aspects of daily life that affect our health.

M: In addition to this, our plenary sessions are truly our flagship. These sessions span from bench to bedside, and are given by the best of the best, the true experts in the field. They pave the way, showing us how we can learn and improve our practice. Environmental science has become an increasingly important part of allergy and immunology, as the exposome has become a large challenge. Sessions exploring the epithelial barrier have been fantastic to attend, as they encompass the fundamental aspect of chronic disease, from basic, to translational, to public health concerns. For those interested in research, we have a huge number of abstract sessions, all unpublished work at the real cutting edge.

However, I must say that the highlight for me is the coming together of the EAACI family that occurs each year at congress. We have a membership of over 15,000, as well as physical participation of over 7,000 from Europe, the USA, and Asia, which demonstrates how we have grown into one of the largest allergy and immunology societies globally.

Putting Guidelines into Practice: Supporting Young People with Hereditary Angioedema to Live Attack-Free

Interviewees:	Matthew Buckland[1,2] 1. Great Ormond Street Hospital (GOSH), London, UK 2. Barts Health NHS Trust, London, UK

Disclosure:	Consultant for BioCryst, CSL, Takeda, and Pharming and/or received unrestricted grant support from them for research.
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Disclaimer:	The opinions expressed in this article belong solely to the named interviewee.
Support:	Publication of this article was funded by BioCryst, who selected the interviewee and have reviewed the article.
Keywords:	Hereditary angioedema (HAE), oedema, prophylaxis, quality of life (QoL), specialist centre.
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Interview Summary

Hereditary angioedema (HAE) is a rare genetic disorder that causes unpredictable, recurrent episodes of cutaneous or submucosal oedema, affecting mainly the skin, abdomen, or upper respiratory tract.

People with HAE often present with their first attack in their early teenage years, but episodes can occur in patients as young as 5 years old. For adolescents and young people, HAE can have a significant impact on quality of life (QoL), affecting social interactions, educational attainment, physical activity, and emotional wellbeing.

Despite the recent development of effective, specific, and well-tolerated medications, which are recommended by international guidelines for treatment and management of the condition, many patients with HAE fail to gain access to specialist care and an appropriate treatment plan that could reduce the number of HAE attacks, and improve their QoL.

EMJ interviewed Consultant Immunologist Matthew Buckland, who oversees children's and families' HAE clinics at Great Ormond Street Hospital (GOSH) and Barts Health NHS Trust, London, UK, to find out what more can be done to support people with HAE. Buckland discussed their experience of managing young patients with HAE and, based on their own practice and experience, outlined how to ensure patients have treatment management plans in place to achieve a good QoL.

INTRODUCTION

The availability of specific licensed medicines to treat acute HAE attacks and prophylactic options to prevent future episodes is changing the way people with HAE are treated, and is giving them hope for a future free from debilitating HAE attacks.[1]

HAE is a rare disease that affects approximately 1:50,000 individuals worldwide.[1] In most cases, it is caused by mutations in the *SERPING1* gene that encodes the C1-esterase inhibitor (C1-INH) protein. The mutations result in an absence or reduction in C1-INH protein, which in turn affects the kallikrein-bradykinin production pathway, and leads to increased vascular permeability and oedema.[2]

Attacks of HAE are unpredictable, and can be life-threatening if the upper airways are involved.[3] Stress, physical injury, and surgery are known triggers, but attacks can happen without warning.[4] Prompt treatment can reduce the severity of attacks, and guidelines recommend that patients carry on-demand medication for the treatment of at least two attacks, and self-administer medication when required.[1]

However, on-demand treatment is often insufficient to achieve complete control of HAE, and effective long-term prophylactic medications that can reduce the risk of attacks and improve QoL are available.[1] Despite revised guidelines to the contrary, some patients are still prescribed attenuated androgens (AA) as prophylaxis for HAE.[5]

EMJ interviewed Consultant Immunologist, Matthew Buckland, to find out what more can be done to support people with HAE, and ensure they receive optimal treatment to achieve a better QoL.

WHAT ARE THE KEY NEEDS OF PATIENTS WITH HEREDITARY ANGIOEDEMA IN YOUR PRACTICE?

I see people with HAE in clinics for families and children at Great Ormond Street Hospital and Barts Health NHS Trust, in London, UK. There's a continuing need for better, age-appropriate information about the disease and its causes, even for families with a long history of HAE.

Effective care plans and medications are crucial to allow children to lead a normal life. How children interact with their peers, engage in activities, sports and so on, is very important. We need to provide adequate and ongoing support to parents and schools as children transition through their developmental stages to independence.

In our clinics, we've tried to standardise the process of assessing patients. We assess children and adults using the Angioedema Control Test (AECT)[6] to monitor how they are responding to therapy and how they react to uncertainty. The unpredictability of attacks is a significant worry for people, particularly those who have a family history including deaths from laryngeal oedema.

WHAT ARE YOUR MAIN CONSIDERATIONS WHEN DECIDING ON TREATMENT APPROACHES FOR PATIENTS?

Each patient is unique, and in HAE there is not a clear genotype-phenotype correlation. Patient preference is very important in our decision making. Then, depending on which country you are practicing in, you will have a set of licensed indications and available treatments to choose from. However, you also have the constraints set by the commissioning body.

There are lots of variables and we must navigate a path through. One patient may tolerate two attacks a month, but another may say they cannot tolerate two attacks a year. In the latter case we do not currently have in the UK a commissioned first-line licensed prophylaxis that could meet that need if they are not currently on treatment. Similarly, there are individuals who are needle-phobic and can't cope with self-injection, and those that would prefer an oral therapy to an injectable one.

A parent's own response to therapy can affect how they make decisions with their children. Conversely, sometimes when children are started on newer therapies, it affects the parental view of how their own HAE could be managed, including requests to change long term prophylaxis (LTP).

HOW DO THE UPDATED INTERNATIONAL TREATMENT GUIDELINES RELATE TO THE PATIENTS YOU SEE?

The arena of therapy and caring for people with HAE has changed significantly in the past 15 years. We now have good licensed and well-tolerated therapies, and clear guidance on their use.[1]

We've moved to the point that individuals should, in most cases, expect to be free from HAE attacks. The guidance recommends three first-line options for prophylaxis; plasma-derived or recombinant C1-INH, lanadelumab, both of which are injectable, and berotralstat, which is administered orally. AAs are no longer recommended as first-line therapy because they carry the risk of significant side effects, and they're not specifically licensed or disease targeting.[1]

The updated guidelines enable us to have a discussion with individuals that focuses around whether they're symptomatic or not, and whether they consider any attacks acceptable. In the UK, at least, this is our starting point for a conversation about long-term prophylaxis. Second-line therapy is only considered in cases where first-line therapies fail, or individuals find the alternatives unacceptable.

WHAT IS THE IMPORTANCE OF LONG-TERM PROPHYLAXIS TO YOUR PATIENTS, ADOLESCENTS, AND YOUNG ADULTS IN GENERAL?

There is a medical need to reduce HAE attack frequency in young people. Almost half of HAE attacks in children result in hospital attendance. It is common for them to experience abdominal attacks that result in vomiting and dehydration.[7] However, parents are often concerned about the use of long-term medication and its implications.

HAE can affect a person's life chances, particularly if it's not managed properly. For example, young people often have a significant increase in their attack frequency when they are studying for, and sitting, exams. We try to plan forward and explain how prophylaxis can help reduce the number of attacks, and how that may help them to sit their exams by removing the worry about the risk of an attack.

WHAT ARE THE BARRIERS FACING CLINICIANS/PATIENTS THAT PREVENT BETTER UPTAKE OF FIRST-LINE RECOMMENDED LONG-TERM PROPHYLAXIS, AND HOW CAN THEY BE OVERCOME?

My job is to encourage individuals to aspire to an optimal quality of life. Patients need the reassurance that this is an achievable goal.

Most pre-pubertal children with HAE are asymptomatic, but as they enter adolescence, the combination of hormonal changes and increased psychological stressors in education and life, can lead to attacks that start to affect their QoL.

In our clinics, when we prescribe berotralstat, to young people (over 12 years of age), who are eligible, it is well tolerated and shows durable benefit. This is supported by new data from the APEX-S study that shows the progressive increase in benefit over time in reducing attack rate, and in improving overall QoL.[8]

Regular review meetings are vital to achieving optimal disease management. Access to specialist centres with experienced multidisciplinary teams can help to ensure patients access optimal support and treatments to meet their individual needs.

I have patients who, when they move onto long-term prophylaxis and become attack-free, are delighted. They say: "I was having a terrible time, and now it's amazing. I can't remember the last time I had an attack."

SOME PATIENTS ARE STILL PRESCRIBED ATTENUATED ANDROGENS TO TREAT HEREDITARY ANGIOEDEMA, DESPITE KNOWN SIDE EFFECTS. WHAT MORE CAN BE DONE TO ACCELERATE THE TRANSITION OF PATIENTS ONTO FIRST-LINE RECOMMENDED ALTERNATIVES?

It is only in extremely rare circumstances that AA should be prescribed to control HAE. For example, if first-line treatments fail, or when the patient is visiting the UK and those medicines are not available in their home country, you might also consider AA as an adjunctive therapy.

In my experience, people who remain on AA are those who are not having informed discussions with a specialist about the risks and benefits of more recently licensed treatments. When I see people like this, I explain that if they were a new patient coming to me, I would offer them the licensed, specific medications that are recommended in the guidelines. In nine out of 10 cases, this is enough for them to want to make the change.

However, transitioning patients to alternative medications and prophylaxis can be complex. In the UK, for example, the commissioning guidance is that a patient should be having two or more attacks a month to be eligible for berotralstat.[1] If you're on AA and having no attacks, you are not automatically eligible. Usually, HAE attacks increase in frequency as AA is tapered off, and this is a concern for the patient.

WHAT MORE CAN BE DONE TO ENCOURAGE CLINICIANS TO CONSIDER RECOMMENDED LICENSED PROPHYLACTIC MEDICATION FOR NEWLY-DIAGNOSED INDIVIDUALS AND THOSE WITH EXISTING HEREDITARY ANGIOEDEMA?

Every clinician should be following the same guidance,[1] but some people with HAE are not under the care of a specialist. This means they are not having those important discussions about the risks and benefits of the treatment they are on.

Raising awareness of rare diseases in primary care is important. Patient support organisations, such as HAE UK, do a fantastic job, and need to continue to encourage people to seek out specialist care, and that will improve take-up of prophylaxis.

International care quality standards exist, and patients should expect their healthcare provider to be accredited in some way, so they know they are receiving an approved standard of care. In England, it's a commissioning requirement for HAE centres to be registered with one such body, Quality in Primary Immunodeficiency Services (QPIDS), and across Europe it is ACARE.

ARE THERE TOOLS AVAILABLE THAT CAN SUPPORT CLINICIANS IN HAVING DISCUSSIONS ABOUT OPTIMAL TREATMENTS FOR PATIENTS?

Any tools that help clinicians to place individuals into groups according to how well controlled their HAE attacks are can help them to start discussions about treatment goals, and whether their QoL could improve with alternative medications.

The AECT[6] is really helpful in assessing how well HAE is being controlled, and the efficacy of any intervention. It gives us a record of a person's health and wellbeing before treatment begins, and then we can monitor progress, including medication tolerability, side effects, and acceptability.

We also encourage people to use our patient-facing information portal. Individuals can access the AECT form from here, and they can also use it to give us a 'heads-up' if they are unhappy with any aspect of their care and want to have a specific discussion. These tools help to form the basis for those all-important discussions about how best to control HAE attacks and optimise QoL.

EU.HAE.00005

Date of Preparation: July 2023

References

1. Maurer M et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2021 revision and update. Allergy. 2022;77(7):1961-90.
2. Santacroce R et al. The genetics of hereditary angioedema: a review. J Clin Med. 2021;10(9):2023.
3. Minafra FG et al. The mortality from hereditary angioedema worldwide: a review of the real-world data literature. Clin Rev Allergy Immunol. 2022;62(1):232-9.
4. Longhurst HJ, Bork K. Hereditary angioedema: an update on causes, manifestations and treatment. Br J Hosp Med (Lond). 2019;80(7):391-8.
5. Riedl MA. Critical appraisal of androgen use in hereditary angioedema: a systematic review. Ann Allergy Asthma Immunol. 2015;114(4):281-8.
6. Weller K et al. Validation of the angioedema control test (AECT) - a patient-reported outcome instrument for assessing angioedema control. J Allergy Clin Immunol Pract. 2020;8(6):2050-7.e4.
7. Nanda MK et al. Clinical features of pediatric hereditary angioedema. J Allergy Clin Immunol Pract. 2015;3(3):392-5
8. Reshef A et al. Berotralstat provides sustained reduction in hae attack rates and improvement in quality of life in adolescent patients: a subgroup analysis. Poster TP-C103. European Academy of Allergy and Clinical Immunology (EAACI) Conference, 9-11 June, 2023.

Interview

David Stukus

Professor of Clinical Pediatrics, Division of Allergy and Immunology; Associate Director, Food Allergy Treatment Center, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, Ohio, USA

Citation: EMJ Allergy Immunol. 2023; DOI/10.33590/emjallergyimmunol/10301359. https://doi.org/10.33590/emjallergyimmunol/10301359.

David Stukus sat down with EMJ to discuss his career as an expert paediatric allergologist, providing insights into the field including the role of social media in healthcare.

Q1 What led you to undertake a career in medicine and specifically in paediatric allergy and immunology?

I studied both molecular biology and psychology as an undergraduate and loved the intersection of understanding how the complexities of the human body interact with those of the human mind. This translated seamlessly towards a career in medicine and specifically paediatrics as I love working with children of all ages. My job is simply fun. Allergy and immunology is a specialty that focuses on some of the most common chronic conditions affecting children such as asthma, food allergies, eczema, and environmental allergies. I love being able to help children and their families by applying my understanding of the immune system to their health.

Q2 In 2011, you started the Complex Asthma Clinic at Nationwide Children's Hospital, Columbus, Ohia, USA, which treats children with severe or difficult-to-treat asthma. What drove you to do this and how has this programme evolved over the years?

Asthma is the leading chronic medical condition, and a top cause of emergency room visits and hospitalisations for children. It's also highly variable in regard to causes and response to treatment. We wanted to provide a focused multispecialty clinic dedicated to helping families who have children with difficult-to-control or severe asthma as they often require a different approach towards diagnosis and management, including more time and resources. Over the past decade, this clinic has grown and offers state of the art treatment with a focus on understanding how the immune system is involved in various types of asthma.

> "Asthma is a top cause of emergency room visits and hospitalisations for children."

Q3 You have focused a lot of your research on food allergy and are Director of the Food Allergy Treatment Center at Nationwide Children's Hospital. What recent advances in the treatment of food allergy are you most excited about?

These truly are exciting times in the area of food allergy as we have new approaches towards diagnosis and management. At our centre, we take an individualised approach to provide the most accurate diagnosis possible, discuss management and risk, and help families with daily decisions that truly impact their quality of life. Oral immunotherapy is one treatment option that can help decrease risk for severe

food allergy reactions from accidental ingestion of small amounts of food allergens. There are additional areas of research that are very exciting and include alternate ways to desensitise through the oral mucosa or skin. In addition, new use of biologic treatments towards food allergy are very promising as well.

Q4 As a board member of the American College of Allergy, Asthma and Immunology (ACAAI), what is your role in this organisation?

It's been an honour for me to serve in various leadership roles with the ACAAI over the past decade, including as a board member for the past 2 years. Our board helps to make decisions surrounding ACAAI initiatives to benefit our members, as well as within the public to help our patients. Our board isn't involved in the day-to-day decisions within the organisation per se, but it helps to steer the ship in regard to advocacy efforts, communication, policy, recruitment into our specialty, and educational offerings such as our annual meeting.

Q5 You strongly value evidence-based medicine and recently published an article on tackling medical misinformation in allergy and immunology practice. What were the key take-away messages from that paper?

I think that it's important for everyone to understand the many ways in which we are all influenced in our decision making. We all have cognitive biases that impact how we receive information, which is now mainly through the internet and social media. Even more importantly, there are many areas where clinical practice is simply outdated and not up to date with current evidence-based guidelines. It's important for clinicians to be aware of how and why inertia impacts the care we offer and also why we need to remain as current as possible in our approach towards diagnosis and management.

Q6 You wrote a book on using social media for medical professionals and are very active on social media yourself. Why do you find this important and what do you aim to achieve through your social media?

Social media has fundamentally changed the manner in which society shares and receives information. Critical thinking skills and the ability to vet information for accuracy is more important than ever. Unfortunately, misinformation and disinformation are everywhere online and truly impact patients in a negative way. I see this in daily practice and online. I hope to provide a source of not only accurate evidence-based information but also perspective to help people better navigate their use of social media.

Q7 What topics do you feel merit greater attention in your specialty and what direction would you like to see future research take?

I'd love to see more progress regarding primary prevention of all forms of allergic conditions. We've made some progress in this realm with food allergy by recommending early introduction of allergenic foods into baby's diets but even this isn't 100% effective. We need better approaches towards asthma, eczema, and environmental allergies.

Q8 Which new technologies and recent breakthroughs do you expect will make a real difference in your field in the near future?

Wearable technology holds promise, particularly for asthma and some of the digital monitoring that has been introduced in recent years. Artificial intelligence is only getting more useful over time and I'm sure will have growing importance in healthcare over the next decade. However, we also need to recognise the limitations of technology and how best to apply it for each individual patient or person. Nothing we do in medicine or public health is one size fits all.

Q9 As an educator, where do you see your focus lie in the coming years?

I love the opportunity to offer education and perspective to various audiences, particularly the general public and primary care clinicians. I'm still relatively young in the grand scheme, yet also recognise that I'm rapidly becoming 'the old guy' to our current generation of trainees. As such, I see my focus transitioning a bit to help others learn from my experience by offering practical approaches towards patient care. I also want to continue to proactively discuss the importance of wellness, gratitude, and priorities to my colleagues and younger generations of healthcare professionals. Having gone through burn out myself, I want to do anything I can to help others on their path.

"Unfortunately, misinformation and disinformation are everywhere online and truly impact patients in a negative way."

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AIT Clinical Relevance: Patients' Benefits All Along the Treatment Journey

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This work has been supported by an institutional grant from Stallergenes Greer.

Early Short-Term Benefits with AIT[3-7]

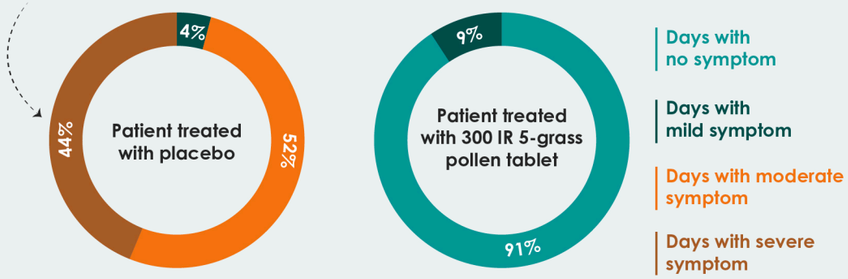
1

Significant reduction in ACSMS of at least -2.31 with the 300 IR 5-grass pollen tablet versus placebo during the pollen period in adults, adolescents, and children with grass pollen-induced ARC.

This difference can be translated into concrete patient outcomes, as illustrated by the patient cases below.

Patients treated with the 5-grass tablet can expect to be free from moderate to severe blocked nose over the pollen period.

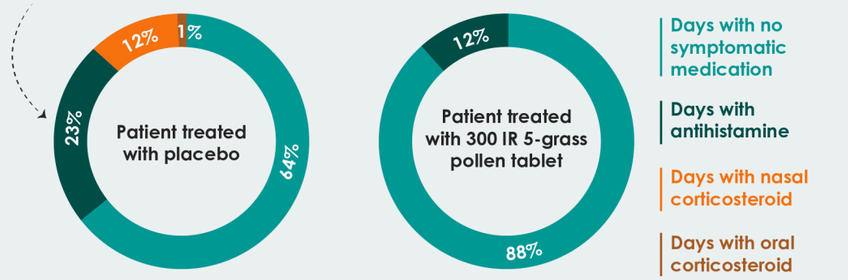
Blocked nose
(considering the five other symptoms of stable severity and use of rescue medication also stable)



% of days with blocked nose over the pollen period (approximately 3 months)

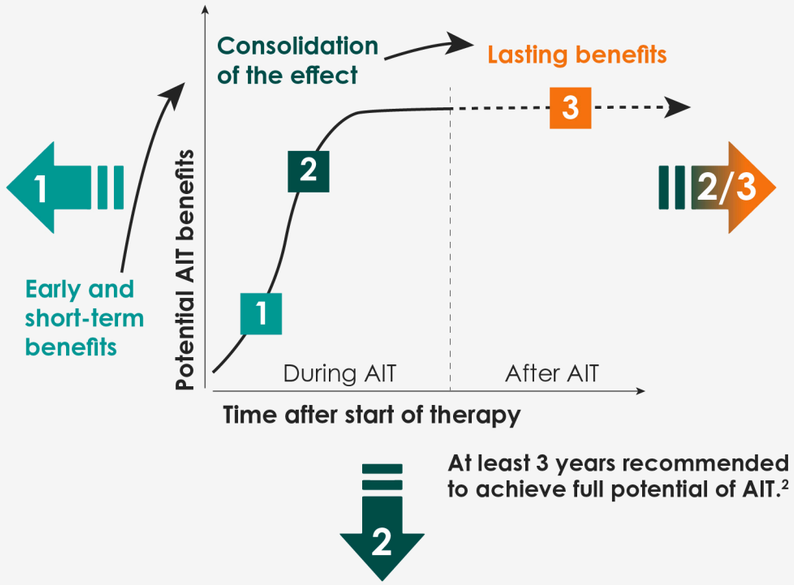
Patients treated with the 5-grass tablet can expect to be free from oral corticosteroid use over the pollen period.

Pharmacotherapy intake
(considering the six symptoms of stable severity)



% of days with medication use over the pollen period (approximately 3 months)

Three Key Milestones in Patient Experience with AIT*[1]



At least 3 years recommended to achieve full potential of AIT.[2]

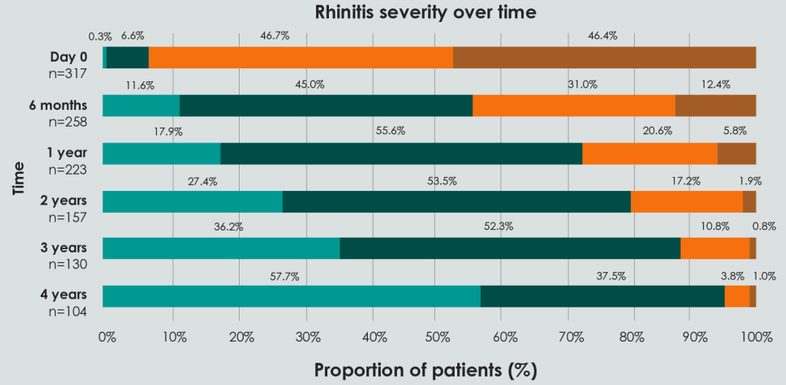
Consolidation of the Effect

2

Japanese Long-Term Real-Life Study[8]

- Prospective, observational study
- 538 patients evaluable for safety and 383 for effectiveness
- 300 IR HDM SLIT tablet administered for up to 4 years in daily practice
- **Objective: Long-term safety and effectiveness evaluation**

Rhinitis severity over time



Asymptomatic | Moderate | Mild | Severe or very severe

95.2% patients were asymptomatic or with mild symptoms at Year 4, confirming the sustained effectiveness of the 300 IR HDM SLIT tablet for up to 4 years of continuous use.

Conclusion

AIT is associated with concrete meaningful patients benefits as early as the first months of treatment with an effect consolidating over time.

In addition, AIT has the potential to halt the allergic march and therefore prevent disease worsening and asthma onset.

In current practice, shared decision making and patient education may improve their adherence and satisfaction with AIT.

Consolidation of the Effect and Lasting Benefits

2 **3**

EfficAPSI Study[9-12]

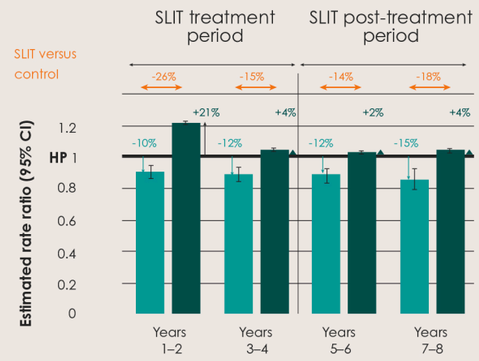
- Real-life, retrospective, pharmaco-epidemiological, longitudinal study using the French National Health data system
- 99,538 SLIT liquid patients and 333,082 non-AIT control patients (SDT only)
- 9 years of follow-up 2010–2018
- **Objective: SLIT liquid impact on asthma onset and HCRU on the long term**

Reduction of the risk of asthma onset with SLIT liquid versus SDT[10]

	Main definition: more sensitive First occurrence of asthma drug dispensing, hospitalisation, or long-term disease for asthma	Secondary definition: more specific First occurrence of hospitalisation or LTD for asthma	Tertiary definition: both sensitive and specific Omalizumab or 3 ICS +/- LABA dispensing or hospitalisation or LTD for asthma
Patients without pre-existing asthma n=69,166	-23%	-34%	-38%

SLIT liquid significantly reduced the risk of asthma onset consistently for all definitions, age groups, and allergens.

Reduction in OCS dispensing in SLIT liquid patients maintained over time versus SDT[11]

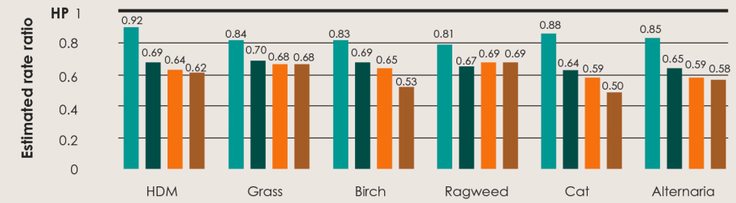


Overtime, OCS dispensing significantly decreased in SLIT patients with a reduction maintained post treatment while it increased in control patients, suggesting a sustained effect of SLIT in patients treated for 2-5 years.

SLIT N=46,815

Control N=190,486

Reduction in INCS dispensing in SLIT liquid patients over time during and after treatment cessation[12]



Consistently for all allergens:

- INCS dispensing significantly decreased by 8%-50% along the study, especially during post-treatment periods
- Similar impact observed for AH but greater decrease for INCS

In control patients with all types of allergens, dispensing over time of INCS and AH decreased by ~10% and increased by up to 50%, respectively

Years 1-2 | Years 5-6 | Years 3-4 | Years 7-8

References

1. Spriggs K et al. J Allergy Clin Immunol Pract. 2023;DOI: 10.1016/j.jaip.2023.02.033.
2. Roberts G et al. Allergy. 2018;73(4) :76S.98.
3. Meltzer E et al. Int J Gen Med. 2010:3:69-91.
4. Klein Tet al. Immunotherapy. Immunotherapy. 2021; 13(14):1193-1204.
5. Pfaar et al. Abstract 100085 . EAACI. 1-3 July. 2022.
6. Brehler et al. Abstract C00234 . EAACI. 9-11 June. 2023 .
7. Liu et al. Allergy Asthma Clin Immunol. 2013:9(1) :30.
8. Okamoto et al. Abstract 000270. EAACI. 9-11 June. 2023.
9. Demoly et al. Abstract 100053. EAACI. 9-11 June. 2023.
10. Devillier et al. Abstract 100051. EAACI. 9-11 June. 2023.
11. Demoly et al. Abstract 100050. EAACI 9-11 June 2023
12. Molimard et al.Abstract 100078. EAACI. 9-11 June. 2023.

Abbreviations

AA: Allergic Asthma; AC:Allergic Conjunctivitis; ACSMS: average combined symptom and medication score; AIT: allergen immunotherapy; AH: antihistamines; AR: allergic rhinitis; ARC: allergic rhinoconjunctivitis; CI: confidence interval; HDM: house dust mite; INCS: intranasal corticosteroid; HP: historical pre-SLIT period; IR: index of reactivity; OCS: oral corticosteroid; SDT: symptomatic drug treatment; SLIT: sublingual immunotherapy.

Footnotes

*AIT is generally prescribed following or in association with symptomatic treatments

The Current Treatment Landscape of Hereditary Angioedema

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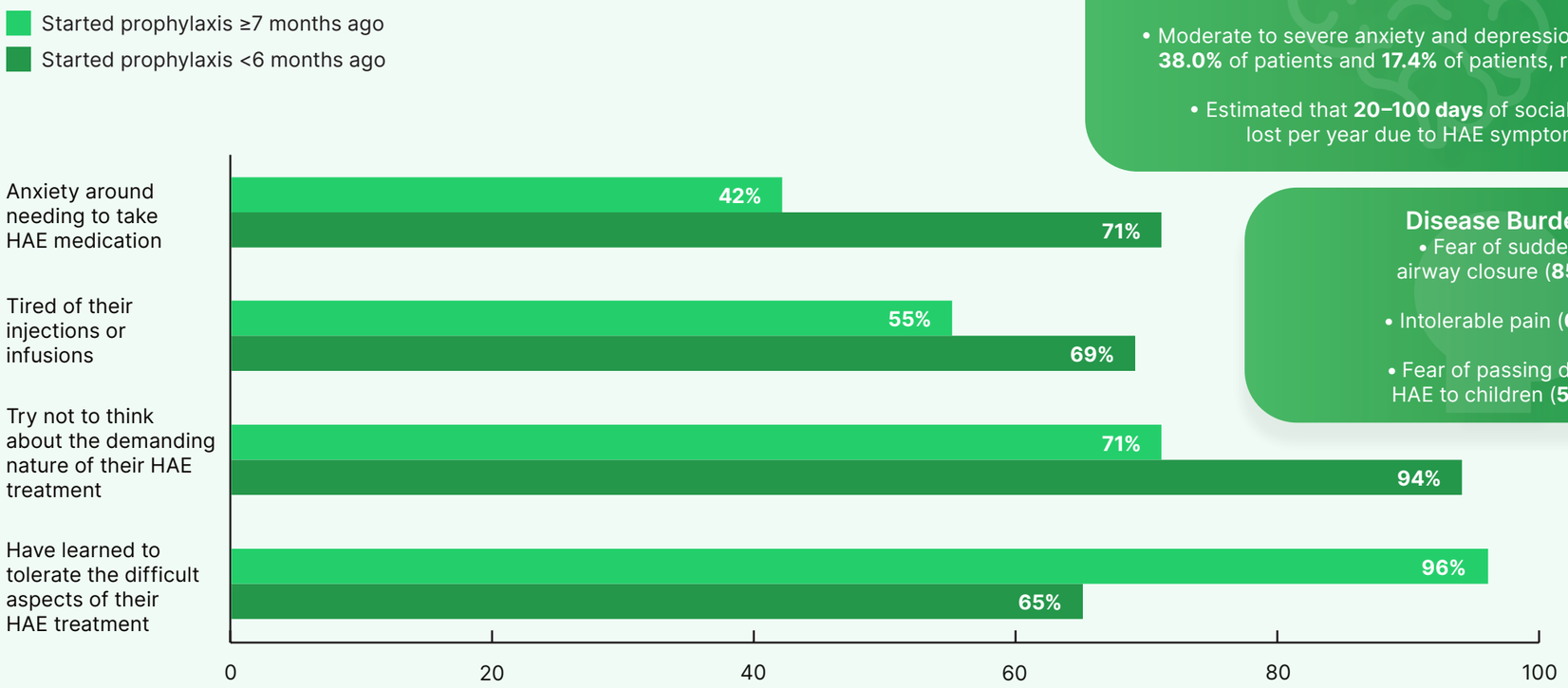
Patient Perspectives on HAE Treatment

Problems with Prophylaxis
Psychological impact of treatment burden on patients with HAE



Impact on Patient QoL

Mental Health

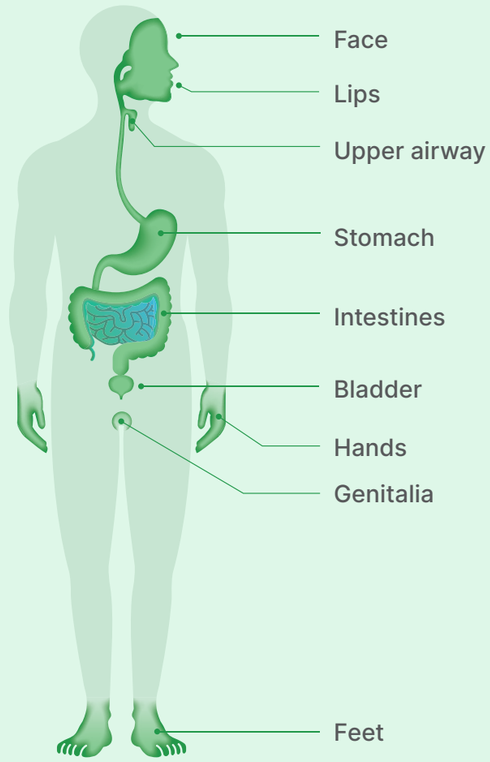
- Score of **13.43** in patient study assessed with HADS scoring system, indicating moderate levels of psychological distress
- Moderate to severe anxiety and depression reported in **38.0%** of patients and **17.4%** of patients, respectively
- Estimated that **20–100 days** of social activity lost per year due to HAE symptoms

Disease Burden

- Fear of sudden airway closure (**85%**)
- Intolerable pain (**65%**)
- Fear of passing down HAE to children (**55%**)

An Overview of HAE

Prevalence: 1 in every 50,000 people
Common HAE swelling sites



Current Treatments for HAE Management

Treatment for Acute HAE Attacks
Current WAO/EAACI guidelines recommend treatment of any HAE attack, regardless of location, to decrease duration and severity.

Early treatment
↓
Shorter period of active symptoms
↓
Shorter attack duration

- Consider patients with HAE-1/2 for self-administration to optimise treatment time
- First-line therapies: intravenous C1-INH, ecallantide, or icatibant
- Surgical intervention is recommended in cases of progressive upper airway oedema

Maintenance Treatment
Long-term prophylaxis

- Should be individualised and considered in all patients with HAE-1/2
- LTP should be monitored regularly through PROs
- First-line therapies: plasma-derived C1-INH, lanadelumab, and berotralstat

Unmet Needs and Future Considerations

- **Many developed PROs yet to be approved by FDA/EMA**
- **No validated PRO measures for use in children with HAE**
- **Optimisation of prophylactic treatments**

→ **93%** of physicians and **86%** of patients reported satisfaction with current treatment, but would be open to treatments that are easier to administer

→ **94%** of physicians and **84%** of patients reported a need for more novel treatments

Key:
C1-INH: C1-inhibitor; EAACI: European Academy of Allergy and Clinical Immunology; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; HADS: Hospital Anxiety and Depression Scale; HAE: hereditary angioedema; HAE-1: hereditary angioedema Type 1; HAE-2: hereditary angioedema Type 2; PRO: patient-reported outcome; QoL: quality of life; WAO: World Allergy Organization.

Bibliography:
1. Zanichelli A et al. The global registry for hereditary angioedema due to C1-inhibitor deficiency. Clin Rev Allergy Immunol. 2021;61:77-83.
2. Longhurst HJ, Bork K. Hereditary angioedema: an update on causes, manifestations and treatment. Br J Hosp Med. 2019;80(7):391-8.
3. Maurer M et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2021 revision and update. Allergy. 2022;77(7):1961-90.
4. Mendivil J et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. Orphanet J Rare Dis. 2021;16(1):94.
5. Savarese L et al. Psychology and hereditary angioedema: a systematic review. Allergy Asthma Proc. 2021;42(1):e1-7.
6. Radojicic C et al. Patient perspectives on the treatment burden of injectable medication for hereditary angioedema. Allergy Asthma Proc. 2021;41:S4-10.
7. Bygum A et al. Disease severity, activity, impact, and control and how to assess them in patients with hereditary angioedema. Front Med (Lausanne). 2017;4:212.
8. Riedl MA et al. Physician and patient perspectives on the management of hereditary angioedema: a survey on treatment burden and needs. Allergy Asthma Proc. 2021;42(3):S17-25.

EMJ

The Danger of Disappearing Allergen Skin Test Substances

Authors: *Stefan Wöhrl,[1] Wolfram Hoetzenecker,[2] Wolfgang Hemmer,[1] Felix Wantke[1]

1. Floridsdorf Allergy Center (FAZ), Vienna, Austria
2. Department of Dermatology, Kepler University Hospital and Medical Faculty, Johannes Kepler University, Linz, Austria

*Correspondence to woehrl@faz.at

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Allergic diseases affect approximately one-quarter to one-half of the average population under 50 years of age in Central Europe.[1] Due to the high proportion of affected individuals, allergy testing needs to be performed on a large scale, with high sensitivity and specificity at a low cost. Skin tests are the most important diagnostic measure fulfilling these requirements: they can be performed immediately and, quite in contrast to laboratory tests, the results of skin prick tests for the diagnosis of immediate allergy (IgE-mediated: Type I) can be assessed, and discussed with the patients 15–20 minutes later. Patients do not need to be called in for a second appointment to discuss the results of serum-based determination of specific IgE. Recently, we demonstrated that the sensitivity of skin prick tests is superior to the measurement of allergen-specific IgE, even for modern molecular allergens.[2] In T cell mediated allergy of the delayed type (contact dermatitis: Type IV), patch tests read after 48–72 hours are the only available diagnostic measure.

Although allergists worldwide recognise the immeasurable value of skin testing as the primary test for more than two-thirds of their patients in their daily work routine,[3] we are faced with the critical situation of a gradual decline in commercially available test preparations. What are the reasons for this development? Allergy diagnosis is a niche market in which medical diagnostic companies generate little financial income.[4] In an effort to improve the quality of diagnostic allergens, the European legislation on medicinal products 2001/83/EC and its refinement in 2007 recognised preparations for allergy skin testing as drugs.[5] While quality and inter-batch reproducibility are laudable goals, European regulation authorities have forgotten that there is no market to compensate for the high economic burden caused by this legislation. Diagnostic test allergens must be registered in the same way as therapeutic allergens that are used as drugs. Once registered, registration must be maintained on a regular basis. If a registered test solution does not become introduced onto the market within a certain time frame, the registration is automatically lost after a few years due to a 'sunset clause'.[6]

Reimbursement for allergy testing by the public healthcare system is very limited and, therefore, the diagnostic industry has not been able to pass on these new costs to allergists.[7] Previously, diagnostics for Type I allergies were considered a by-product of allergen manufacturers, and revenue from the sales of allergen solutions for allergen-specific immunotherapy cross-funded diagnostics. Therefore, it was clear from the beginning that the first implementation of the European law into a national law, which occurred in the most important allergen market in Germany in 2008,[8] risked to reduce the number of available solutions due to the high administrative costs. However, no one anticipated that the industry would drastically withdraw diagnostic allergens within the first few years of the new legislation coming into effect. Between 2011 and 2018, the number of approved skin prick test solutions for immediate-type allergies in Germany decreased from 522 to 378 (-27%) and for delayed-type allergies from 343 to 132 (-61%).[9]

In 2017 there was also a revision of the European '*In-Vitro* Diagnostic Device Regulation' (IVDR 2017/746), which came into force on 26th May 2022, without the need for translation into national law.[10] The reason for this was to prevent future medical fraud such as the Theranos scandal. Ultimately, this has the same consequences for niche allergology products as the legislation on *in vivo* diagnostics.[11] Again, allergology is faced with the decline of *in vitro* tests for rare allergens. Consequently, the loss of *in vivo* testing cannot be replaced by switching to *in vitro* testing systems. This is especially problematic in the field of occupational medicine, where only a small number of patients are affected and subsequently tested.[12]

Skin testing is currently 'under fire'. On the one hand, existing diagnostic allergens have been withdrawn from the market; on the other hand, hardly any new skin tests have come onto the market for two decades. Patch tests in particular are in a 'frozen' state, with the introduction of new allergens already dating back to the early 2000s.[13]

As a countermeasure, the European Academy of Allergy and Clinical Immunology (EAACI) has drawn up a position paper listing the most important requirements to European policy makers to maintain and hopefully even increase the availability of diagnostic allergens.[14] The most important points include: simplification of the approval process for new diagnostic allergens; the homologous groups principle, meaning that not every single allergen from the same allergen family requires a full dossier for market authorisation; fee reduction of marketing authorities; and increased reimbursement schemes in national healthcare systems to compensate the increasing costs of skin testing (not only the diagnostic allergens, but also the recent enormous increase in labour costs for highly specialised and trained health personnel in allergology).

How could we get out of that situation? By going back to the way we did it a long time ago and making the skin prick test solutions ourselves again, without any standardisation? In a recent study, a Dutch group compared five 'homemade' extracts with commercially available food extracts from one of the largest allergen manufacturers still available at the time. They found mixed results with a good correlation for hazelnut and walnut extracts, but not for apple, peanut, and peach.[15] Thus, 'homemade' extracts may not be the way to go.

Another approach could be to minimise skin prick test panels, since many standard panels test the major inhalant allergens twice, e.g., birch pollen plus hazelnut pollen from beech trees, or *Dermatophagoides pteronyssinus* plus *Dermatophagoides farinae* from the house dust mites. When applying the concept of cross-reactivity within homologous allergen families, it is sufficient to use only one representative of an allergen family.[16]

Not all is lost, yet. A new European Union (EU) guideline 'Recommendation on common regulatory approaches for allergen products' (Co-ordination group for Mutual recognition and Decentralised procedures – human [CMDh]/399/2019) has been implemented to overcome this situation.[17] The new CMDh guideline may open a small window, as diagnostic allergens for *in vivo* skin testing will be treated somewhat less stringently than allergen products to be used as therapeutics.[17]

Table 1: Allergen sources for which full marketing authorisation is required according to Annex I of Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh)/399/2019.[17]

Pollen of the sweet grasses (Poaceae)
Pollen of the beech tree group (birch, hazelnut, elder, beech, oak)
Pollen of the oil tree group (olive, ash)
Pollen of the cyprus tree
Ragweed pollen (*Ambrosia*)
Pellitory pollen (*Parietaria*)
House dust mites (*Dermatophagoides*)
Bee and wasp venom (*Hymenoptera*)
Cat (*Felis domesticus*)
Peanut (*Arachis hypogaea*)
Peach Fruit (*Prunus persica*)

Nevertheless, the following allergens require full marketing authorisation, as mentioned in Annex I of CMDh/399/2019, regardless of whether they are used for diagnostic or therapeutic purposes (Table 1). An originally included Annex II, which listed additional or rarer allergens, was deleted at the request of many experts during the public consultation on this guideline.

We can only hope that these changes will make a difference before the last available standardised skin test allergen for the diagnosis of immediate allergies (prick tests) and delayed allergies (patch tests) will have become 'extinct'.

References

1. Kölli F et al. Aero-allergen sensitization in the general population: longitudinal analyses of the LEAD (Lung Heart Social Body) study. J Asthma Allergy. 2022;15:461-73.
2. Gureczny T et al. Allergy screening with extract-based skin prick tests demonstrates higher sensitivity over in vitro molecular allergy testing. Clin Transl Allergy. 2023;13(2):e12220.
3. Cardona V et al. Current practice of allergy diagnosis and the potential impact of regulation in Europe. Allergy. 2018;73(2):323-7.
4. Asero R, Cecchi L. Allergy diagnostics: where are we going? Eur Ann Allergy Clin Immunol. 2020;52(6):243-4.
5. European Medicines Agency (EMA). Guideline on allergen products: production and quality issues. 2008. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-allergen-products-production-quality-issues_en.pdf. Last accessed: 5 June 2023.
6. Mahler V. Testallergene: Aktueller Stand der Verfügbarkeit aus regulatorischer Sicht. Dermatologie in Beruf und Umwelt. 2018;66(7):140-4.
7. Klimek L et al. Diagnostic test allergens used for in vivo diagnosis of allergic diseases are at risk: a European perspective. Allergy. 2015;70(10):1329-31.
8. Bundesministerium der Justiz. Verordnung über die Ausdehnung der Vorschriften über die Zulassung der Arzneimittel auf Therapieallergene, die für einzelne Personen aufgrund einer Rezeptur hergestellt werden, sowie über Verfahrensregelungen der staatlichen Chargenprüfung (Therapieallergene-Verordnung). 2008. Available at: https://www.gesetze-im-internet.de/tav/BJNR217700008.html. Last accessed: 5 June 2023.
9. Klimek L, Zuberbier T, "Problematik der Diagnostikallergbene," Klimek L et al. (eds.) Weißbuch Allergie in Deutschland (2019) 4th edition, Heidelberg: Springer Berlin, pp.253-61.
10. Stenzinger A, Weichert W. Einfluss der neuen In-vitro-Diagnostik-Regulation (IVDR) der Europäischen Union auf die Pathologie. Was ist wichtig? Pathologe. 2020;41(Suppl 2): 129-33.
11. Vanstapel F et al. ISO 15189 is a sufficient instrument to guarantee high-quality manufacture of laboratory developed tests for in-house-use conform requirements of the European *In-Vitro*-Diagnostics Regulation. Clin Chem Lab Med. 2023;61(4):608-26.

12. Mahler V. Neue Allergene für die Berufsdermatologie? Hautarzt. 2021;72(6):474-83.
13. Becker D. Neue Kontaktallergene für die Epikutantestung. Hautarzt. 2009;60(1):22-5.
14. Klimek L et al. In-vivo diagnostic test allergens in Europe: a call to action and proposal for recovery plan-an EAACI position paper. Allergy. 2020;75(9):2161-9.
15. Terlouw S et al. Homemade food allergen extracts for use in skin prick tests in the diagnosis of IgE-mediated food allergy: a good alternative in the absence of commercially available extracts? Nutrients. 2022;14(3):475.
16. Eder K at al. Does the principle of homologous groups allow a reduction of allergens in the skin prick test panel? Eur Arch Otorhinolaryngol. 2020;278(1): 117-25.
17. Bonertz A et al. New guidance on the regulation of allergen products: key aspects and outcomes. Curr Opin Allergy Clin Immunol. 2020;20(6):624-30.

The Role of Co-Factors in Mast Cell Activation

Authors:	*Michael Rudenko[1] London Allergy and Immunology Centre, Harley Street Allergy Clinic, London, UK *Correspondence to info@ukallergy.com

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MAST CELL INTERACTIONS WITH NERVOUS SYSTEM

Degranulation of activated mast cells affects many conditions and can modulate physiological and pathological responses. Mast cells are mostly located around blood vessels and sensory nerves.[1] They derive from myeloid lineage and reside in connective tissues.[2] Mast cells are granulocytes that have heterogenous phenotypes, and were originally named by Paul Ehrlich in 1879.[3]

The main role of mast cells as a part of the innate immune system lies within innate and adaptive immune responses, participating in the immune mechanisms, and protecting against viral and bacterial threats.[1] Many conditions ranging from urticaria to anaphylaxis, as well as autoimmune conditions, have mast cells in the pathophysiology.[3]

Mast cells recognise injured tissues with the help of receptors in association with the epithelium and activate initial inflammatory responses.[4] They play a role in tissue repair and angiogenesis, and are mainly responsible for antiparasitic immune responses through the mechanisms of vasodilation and activation of nervous system.[5]

These responses are influenced by cytokines, as well as other humoral factors within the body.[3]

In the barrier tissues mast cells release pro- and anti-inflammatory mediators that can either be preformed and kept in granules, or produced.[6] Mast cells can be activated via FcεRI receptors bound to specific IgE molecules or with the help of toll-like receptors, IgG receptors, and receptors to components of complement.[7]

A range of medicators can stimulate sensory nerve receptors, including protease-activated receptor-2, histamine 1–4-receptors, IL-31 receptors, and high-affinity nerve growth factor receptors.[8]

In an allergic reaction, the allergen crosslinks two neighbouring IgE molecules (specific to that particular protein) bound to receptors on the surfaces of basophils and mast cells, leading to release of medicators.[9]

Mast cells may be activated by allergens/auto-allergens or IgG antibodies against IgE or its receptor. Activation by the autoimmune mechanism can happen through binding IgG anti-IgE with the α subunit of adjacent IgE receptors on mast cells.[10]

Complement activation by immune complexes can result in release of complement 3a, complement 4a, and complement 5a anaphylatoxins that can cause histamine release via an IgE independent mechanism.[11] It was shown that degranulation of mast cells via anaphylatoxins is restricted to certain subpopulations of mast cells because mucosal mast cells do not express anaphylatoxin receptors.[12]

Reciprocal interactions between sensory nerves and mast cells happen via vasoactive intestinal peptides and neuropeptides (substance P), leading to stimulation and degranulation of mast cells potentiation of pruritus and inflammatory response.[13] In chronic skin conditions that include allergic contact dermatitis, atopic dermatitis, and psoriasis, as well as urticaria and angioedema, intense itch occurs as a result of links between mast cells and sensory nerves in the state of neurogenic inflammation in the skin. Pruritus can be exacerbated by endogenous and exogenous co-factors.[14]

ROLE OF CO-FACTORS FOR BASOPHILS AND MAST CELLS

Physical factors known as co-factors include exercise exceeding the standard daily routine, alcohol, non-steroidal anti-inflammatory medication, and heat or change in temperature, as well as other factors that can range from increased stress levels, changes in hormonal levels (menstruation), or consequences of an infection. Genetic background may contribute in creating clinically relevant predisposition to particular conditions.[15]

The presence of co-factors may explain why some patient can tolerate an allergen in some circumstances but in others the same patients develop a severe anaphylactic reaction. Co-factors can influence basophils and mast cells, leading to mediator release.[16]

In the presence of certain co-factors less quantity of allergen might be required to cause clinical symptoms.[17]

According to literature co-factors may have contributed to up to 30% of episodes of anaphylaxis in adults. Epidemiological studies demonstrated that 39% of severe reactions were triggered by co-factors and the most frequent were due to exercise, alcohol, non-steroidal anti-inflammatory drugs, and infections.[18] Exercise can influence adenosine and eicosanoid metabolism, and increase plasma osmolarity associated with redistribution of blood flow.[19]

It should be especially recommended to avoid the combined intake of identified food allergens and non-steroidal anti-inflammatory drugs, because they action through inhibition of cyclooxygenase and production of prostaglandin E_2, and can exacerbate allergy symptoms.[20]

Mast cells and basophils can be activated by alcohol as a co-factor as it relaxes tight junctions in gut epithelium, leading to an increase in intestinal protein absorption, and especially for small proteins, an alcohol-dependent increase in the intestinal absorption. In approximately 10% of patients alcohol consumption is linked with an increase in food allergy manifestations.[21]

Pseudoallergens can also influence mast cells. These include preservatives and colourings used in a range of foods, alongside dysbiosis in the gastrointestinal tract, deficiency of vitamin D, and changes in iron status profile.[22]

Knowledge about co-factors is important in prevention during allergen-specific immunotherapy. The role of infections as co-factors must be assessed during treatment. Immunotherapy can be paused and the allergen dose can be reduced to avoid co-factor effect in case of an infection.[15]

Proton pump inhibitors and Type 2 antihistamines, due to the mechanism of their action, can reduce the concentration of gastric acid in the stomach, which can be important for patients with oral allergy syndrome to acid-sensitive allergens, making them at risk of developing a systemic reaction following high allergen intake while taking the above medications.[23]

CO-FACTORS INDUCED GLUTEN ALLERGY

A separate condition is wheat-dependent, exercise-induced, IgE-mediated anaphylaxis,

related to consumption of wheat products and engaging in physical activity. In a sensitised individual the symptoms can vary and range from mild pruritus, urticaria, and angioedema to a full-blown anaphylaxis. They only occur when several conditions are met and will only arise within 2 hours of consumption of gluten (omega 5-giladin)-containing food and exposure to a co-factor or combination of co-factors.[24,25]

The common symptoms of mast cell activation include pruritus, hypotension, loss of consciousness following or during exercise, urticaria, angioedema, flushing, and respiratory and gastrointestinal symptoms. They can be exacerbated by a recent or chronic infection.[26-30]

Co-factors, including exercise and alcohol, might lower the threshold for IgE-mediated mast cell degranulation, increase allergen permeability in the gastrointestinal tract and osmolality, and redistribute blood flow.[27,31,32]

There is a hypothesis that sensitisation to gluten occurs through the damage of intact skin in the form of gluten-containing protein fragments in cosmetic products. Among wheat proteins, omega 5-gliadin and high-molecular-weight glutenin subunits were shown to be the major allergens.[28,33-36]

Better understanding of the underlying processes leading to co-factor induced histamine release will allow us to develop avoidance strategies and new treatments, and give better advice to our patients.

References

1. Krystel-Whittemore M et al. Mast cell: a multi-functional master cell. Front Immunol. 2016;6:620.
2. Kolkhir P et al. Urticaria. Nat Rev Dis Primers. 2022;8(1):61.
3. Ehrlich P. Beiträge zur Kenntniss der granulirten Bindegewebszellen und der eosinophilen Leukocythen. Archiv für Physiologie. 1879;166-9.
4. Rudenko M. Central role of mast cells in mastocytosis, hereditary α-tryptasemia, mast cell activation syndrome, urticaria, and angioedema. EMJ. 2022;7(1):90-7.
5. Kaplan AP. Angioedema. World Allergy Organ J. 2008;1(6):103-13.
6. Wölbing F et al. About the role and underlying mechanisms of cofactors in anaphylaxis. Allergy. 2013;68(9):1085-92.
7. Sánchez-Borges M et al. Cofactors and comorbidities in patients with aspirin/NSAID hypersensitivity. Allergol Immunopathol. 2017;45(6):573-8.
8. Süß H et al. Contact urticaria: frequency, elicitors and cofactors in three cohorts (Information Network of Departments of Dermatology; Network of Anaphylaxis; and Department of Dermatology, University Hospital Erlangen, Germany). Contact Dermatitis. 2019;81(5):341-53.
9. Muñoz-Cano R et al. Mechanisms, cofactors, and augmenting factors involved in anaphylaxis. Front Immunol. 2017;8:1193.
10. Christensen MJ et al. Exercise-induced anaphylaxis: causes, consequences, and management recommendations. Expert Rev Clin Immunol. 2019;15(3):265-73.
11. Costanzo G et al. Cofactors, age at onset, allergic comorbidities and gender are different in patients sensitized to omega-5 gliadin and Pru p 3. Sci Rep. 2022;12.
12. Benito-Garcia F et al. Diagnosis and prevention of food-dependent exercise-induced anaphylaxis. Expert Rev Clin Immunol. 2019;15(8):849-56.
13. Li PH et al. Differences in omega-5-gliadin allergy: East versus West. Asia Pac Allergy. 2020;10(1):e5.
14. Siiskonen H, Harvima I. Mast cells and sensory nerves contribute to neurogenic inflammation and pruritus in chronic skin inflammation. Front Cell Neurosci. 2019;13:422.
15. Muñoz-Cano R et al. Immune-mediated mechanisms in cofactor-dependent food allergy and anaphylaxis: effect of cofactors in basophils and mast cells. Front Immunol. 2021;11:623071.
16. Makris M et al. Editorial: the complexity of urticaria. Front Allergy. 2023;4:1149540.
17. Maheshwari A et al. Chronic spontaneous urticaria: an etiopathogenic study. Indian J Dermatol. 2022;67(1):92.
18. Oguz Topal I et al. Does replacement of vitamin D reduce the symptom scores and improve quality of life in patients with chronic urticaria? J Dermatolog Treat. 2016;27(2):163-6.
19. Kolkhir P et al. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. J Allergy Clin Immunol. 2017;139(6):1772-81.
20. Hossein Zadeh Attar M et al. The CD63 basophil activation test as a diagnostic tool for assessing autoimmunity in patients with chronic spontaneous urticaria. Eur J Dermatol. 2019;29(6):614-8.
21. Chanprapaph K et al. Thyroid autoimmunity and autoimmunity in chronic spontaneous urticaria linked to disease severity, therapeutic response, and time to remission in patients with chronic spontaneous urticaria. Biomed Res Int. 2018;2018:9856843.
22. Bansal CJ, Bansal AS. Stress, pseudoallergens, autoimmunity, infection and inflammation in chronic spontaneous urticaria. Allergy Asthma Clin Immunol. 2019;15:56.
23. Kinoshita Y et al. Advantages and disadvantages of long-term proton pump inhibitor

use. J Neurogastroenterol Motil. 2018;24(2):182-96.

24. Kulumbegov B, Gotua M. Case report-wheat-dependent exercise-induced anaphylaxis in a patient with chronic spontaneous urticaria: a diagnostic challenge. SAGE Open Med Case Rep. 2023;DOI:10.1177/2050313X231175851.
25. Asaumi T, Ebisawa M. How to manage food dependent exercise induced anaphylaxis (FDEIA). Curr Opin Allergy Clin Immunol. 2018;18(3):243-7.
26. Asaumi T et al. Provocation tests for the diagnosis of food-dependent exercise-induced anaphylaxis. Pediatr Allergy Immunol. 2016;27(1):44-9.
27. Morita E et al. Food-dependent exercise-induced anaphylaxis. J Dermatol Sci. 2007;47(2):109-17.
28. Aihara M et al. Food-dependent exercise-induced anaphylaxis: influence of concurrent aspirin administration on skin testing and provocation. Br J Dermatol. 2002;146(3):466-72.
29. Cardona V et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10):100472.
30. Caslin HL et al. Controlling mast cell activation and homeostasis: work Influenced by Bill Paul that continues today. Front Immunol. 2018;9:868.
31. Yokooji T et al. Characterization of causative allergens for wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat proteins in facial soap. Allergol Int. 2013;62(4):435-45.
32. Takahashi H et al. Recombinant high molecular weight-glutenin subunit-specific IgE detection is useful in identifying wheat-dependent exercise-induced anaphylaxis complementary to recombinant omega-5 gliadin-specific IgE test. Clin Exp Allergy. 2012;42(8):1293-8.
33. Morita E et al. Food-dependent exercise-induced anaphylaxis -importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis complementary to recombinant omega-5 gliadin-specific IgE test. Allergol Int. 2009;58(4):493-8.
34. Chinuki Y, Morita E. Wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat protein in soap. Allergol Int. 2012;61(4):529-37.
35. Brockow K et al. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. Allergy Clin Immunol. 2015;135(4):977-84.
36. Scherf KA et al. Wheat-dependent exercise-induced anaphylaxis. Clin Exp Allergy. 2016;46(1):10-20.

Drug-Induced Thrombocytopenic Purpura: A Systematic Review and Meta-analysis of Case Reports

Editor's Pick

This article presents a good review of drug-induced thrombocytopenic purpura, which is often under-diagnosed and could be very critical in some patients due to internal and external bleeding. The associated symptoms could interfere with the patient's compliance or adherence to a particular drug essential to them, including antibiotics, monoclonal antibodies, antiplatelets, and disease-modifying antirheumatic drugs. The promotion of early detection and raising clinicians' awareness of drug-induced thrombocytopenic purpura could prevent this adverse event.

Jacques Bouchard
Associate Professor of Clinical Medicine, Laval University, Québec, Canada

Authors:	Ankit Bhardwaj, *Rachna Gupta Department of Pharmacology, University College of Medical Sciences, New Delhi, India *Correspondence to drrachna1@rediffmail.com
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Abstract

In the present systematic review and meta-analysis, the authors analysed case reports of drug-induced thrombocytopenia/drug-induced thrombocytopenic purpura (DITP) and its mechanisms. The search included electronic databases for case reports of DITP using specific keywords in MEDLINE via PubMed, PubMed Central, and Embase. All case reports were designated a score/criteria (definite, probable, or possible). The mechanism of DITP was also analysed in each case report.
A total of 751 case reports were included in the meta-analysis. The incidences for all-score DITP by random and common effect models were 0.65% (95% confidence interval: 0.61–0.69) and, 0.65% (95% confidence interval: 0.62–0.68), respectively. The number of DITPs with scores of 1, 2, and 3 was found in 151, 300, and 300 patients, respectively. Amongst the drugs, the maximum number of DITPs were caused by antibiotics, antimalarials, monoclonal antibodies, antiplatelet

drugs, disease-modifying antirheumatic drugs, anti-epileptics, anti-cancer chemotherapeutics, and non-steroidal anti-inflammatory drugs. Out of 751 cases, 478 patients were hospitalised, and 323 patients had external or internal bleeding, including 62 patients who had major bleeding intracranially or retroperitoneally and required transfusion of two or more units of red blood cells. Mortality occurred in 12 patients. Clinicians should be aware of the potential of drugs causing DITP as an important adverse event, as it may affect patient compliance and adherence to drugs. Unrecognised DITP may lead to severe thrombocytopenia and inappropriate patient management.

Key Points

1. Drug-induced thrombocytopenia/drug-induced thrombocytopenic purpura (DITP) is a potentially fatal adverse effect of drugs, which could be associated with external or internal bleeding varying from mild to severe. DITP affects patient compliance and adherence to drugs.

2. The present systematic review and meta-analysis analysed case reports of DITP. The drugs found to be commonly associated with DITP included antibiotics, monoclonal antibodies, antiplatelets, and disease-modifying antirheumatic drugs.

3. Early detection and clinicians' awareness of DITP could prevent this adverse event, and result in the proper management of patients.

INTRODUCTION

Drug-induced thrombocytopenia/drug-induced thrombocytopenic purpura (DITP) is a potentially fatal side effect that is often under-recognised, and is characterised by immunogenic drug-dependent antibodies and non-immunogenic causing destruction of the platelets when the responsible drug is ingested or injected. Some of these antibodies are already present in a non-reactive form in the absence of a drug, but strongly bind to particular epitopes on platelet membrane glycoproteins (GP) IIb/IIIa or Ib/IX9 when the sensitising agent is available in soluble form. The mechanism could be platelet production inhibition, and/or favouring their elimination, or destruction from the peripheral blood. Cytotoxic drugs suppress overall haematopoiesis or affect megakaryocytopoiesis, which either causes increased platelet consumption/destruction or impaired platelet production.[1]

Numerous medications, including antimicrobials, non-steroidal anti-inflammatory drugs (NSAID), anticonvulsants, and sedatives have been linked to causing thrombocytopenia. Generally, low-molecular-weight drugs like penicillin and penicillin derivatives are considered more immunogenic, causing the production of drug (hapten)-specific antibodies, which are covalently attached to a carrier protein. These drugs *in vivo* may have been connected to certain membrane proteins, which were further identified as foreign particles by the immune system, resulting in the formation of drug-specific antibodies. On subsequent ingestion, the medication can reassociate with the membrane protein to produce an antibody target, leading to the destruction of the blood cells.

Skin bruises, petechiae, epistaxis, or more severe symptoms, including purpura, gum bleeding, gastrointestinal or urinary tract bleeding, and pulmonary haemorrhage can all be signs of DITP.[2]

Major bleeding is described as intracranial, retroperitoneal, or overt bleeding that requires the transfusion of at least two units of packed red blood cells, or results in an immediate haemoglobin drop of 2 g/dL.[3] The lack of a standardised definition for thrombocytopenia,

confirmatory testing, and voluntary reporting leads to under-report of cases of DITP. Clinically, it is challenging to differentiate between idiopathic thrombocytopenic purpura and other thrombocytopenia-causing conditions, such as concurrent sepsis or use of heparin products, which are further increased in patients with multiple comorbidities who are taking multiple drugs.[4] Evidence is lacking with regard to the category of drugs and their association with DITP and its mechanism.

Hence, this systematic review and meta-analysis was undertaken with the objective to analyse case reports of the potential drugs, such as antibiotics, antimalarials, monoclonal antibodies, antiplatelets, disease-modifying anti-rheumatic drugs (DMARD), anti-epileptics, anti-cancer chemotherapeutics, NSAIDs, histamine-2 (H2)-blockers, anti-arrhythmics, antipsychotics, diuretics, anti-hypertensives, and vaccines associated with DITP. The authors also describe the mechanisms of DITP.

METHODS

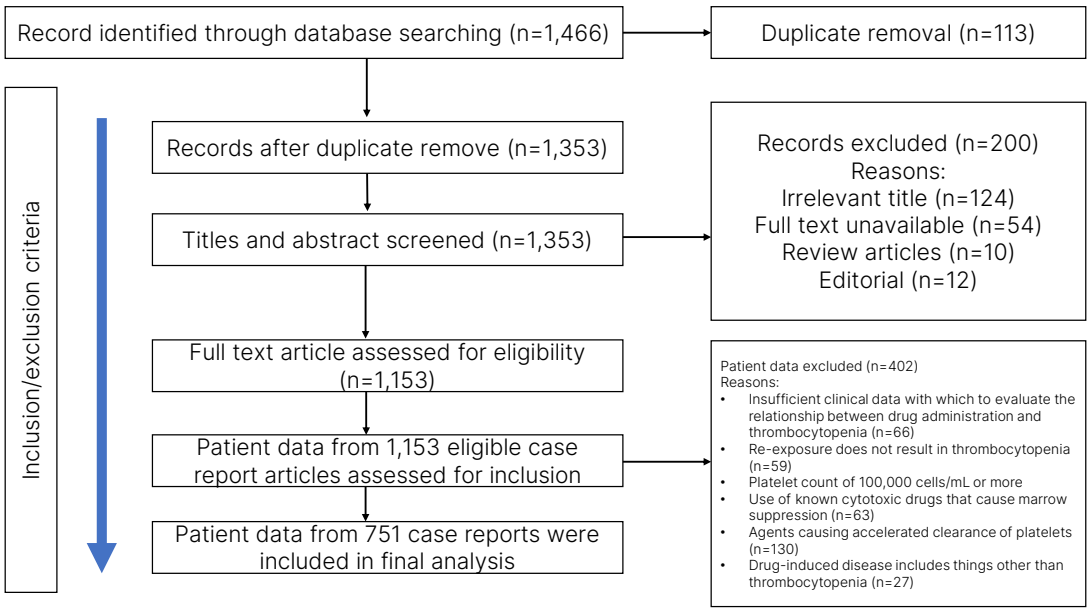
Search Strategy

Electronic databases were searched, including MEDLINE via PubMed, Pubmed Central, and EMBASE, for case reports of DITP. The search process was conducted using the following keywords: "drug-induced purpura," "drug-induced thrombocytopenia," "drug-induced maculopapular rashes," and "adverse-drug skin reaction, skin manifestations OR cutaneous manifestations OR urticaria OR skin disease OR skin lesions". The references of relevant case reports were also reviewed for other potentially suitable studies. The preferred reporting items for systematic review and meta-analysis (PRISMA-2020) were followed for the study design (Figure 1).[5]

Data Extraction

Literature retrieval, screening of the eligible studies, and data extraction of case reports were done by two authors independently, based on the title and abstract according to predefined criteria. Thereafter, they examined the full texts of the articles to achieve maximum reliability and preparation, co-interventions, and follow-up if available.

Figure 1: PRISMA diagram describing the case selection process.



All case reports were assessed for patient characteristics, including age; sex; drug history; symptoms; bleeding definition; whether the patient required hospitalisation or not; and score, based on causality assessment as definite, probable, and/or possible. Any disagreements in selection or extraction were resolved by consensus.

Inclusion and Exclusion Criteria

The authors evaluated all case reports that were about DITP without any age or sex restriction. Studies reported sufficient data describing analysis, including confirmed drugs, bleeding or no bleeding, severity of bleeding, clinical symptoms, laboratory findings, outcomes, diagnostic methods, and treatment.

Inclusion criteria included: the candidate drug preceded thrombocytopenia and recovery from thrombocytopenia was complete and sustained after the drug was discontinued; re-exposure to the candidate drug resulted in recurrent thrombocytopenia; the candidate drug was the only drug used prior to the onset of thrombocytopenia, or other drugs were continued or reintroduced after discontinuation of the candidate drug with a sustained normal platelet count; and other aetiologies for thrombocytopenia were excluded.

Exclusion criteria included: case reports that did not provide clinical data to assess the association between medication administration and thrombocytopenia; case reports with platelet counts of 100,000 cells/mL or more; case reports with drugs having cytotoxic action, known to inhibit bone marrow and induce other abnormalities, such as aplastic anaemia, or thrombotic thrombocytopenic purpura-haemolytic uremic syndrome, and known to speed up the platelet clearance process; and cases in which a patient was exposed to non-therapeutic agents like environmental pollutants, illicit drugs, drug overdose, and drugs not currently in use.

CLASSIFICATION OF CASE REPORTS BASED ON THE MECHANISM OF DRUG-INDUCED THROMBOCYTOPENIA

Systematic Review

The authors systematically reviewed all published case reports of DITP and classified them into six groups on the basis of the mechanism of thrombocytopenia. Group 1 included drug-dependent antibodies; Group 2 autoantibody induction; Group 3 drug-specific antibodies; Group 4 fibrinogen receptor antagonist-dependent antibodies; Group 5 hapten-dependent antibodies; and Group 6 bone-marrow suppression and toxicity.

Criteria for article score: score 1–5 was given to each article as follows. Score 1: thrombocytopenia is definitely caused by a drug and inclusion criteria 1, 2, and 3 fulfilled; score 2: thrombocytopenia is likely brought on by medication, and inclusion criteria 1, 3, and 4 were fulfilled; score 3: thrombocytopenia possibly caused by medication, and inclusion criterion 1 was fulfilled; score 4: drug use is unlikely to induce thrombocytopenia; and score 5: when inclusion criterion 1 is not satisfied or pre-exposure does not induce thrombocytopenia.

A further three levels of association according to the following criteria were analysed in case reports. Firstly, ‘definite’ causal association of drug with thrombocytopenia, which required four criteria to be fulfilled: suspected drug preceded thrombocytopenia, and recovery from thrombocytopenia was complete and sustained after the drug was discontinued; the suspected drug was the only drug used prior to the onset of thrombocytopenia, or other drugs were continued or reintroduced with a sustained normal platelet count; other aetiologies for thrombocytopenia were reasonably excluded; and re-exposure to the suspected drug resulted in recurrent thrombocytopenia. Secondly, a ‘probable’ association required three criteria (1, 2, and more). Thirdly, a possible association if criterion 1 was met but criteria 2 and 3 were not met, the drug was interpreted as having a ‘possible’ association. The authors did not incoclude an analysis of lab reports for drug-dependent antibodies in this meta-analysis.

Meta-analysis

The data for each case report included in the analysis will be provided on demand. To estimate the proportion of reported cases of DITP, the authors performed a meta-analysis for the estimation of the summary effect. The R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) meta-package (metaprop and forest function) was used for data analysis. Drugs were classified based on the mechanism of DITP, and further models were selected based on heterogeneity among the mechanisms of DITP, as assessed using the Q statistic. $P<0.10$ was taken as the significance level. The I^2 statistic was also calculated to measure heterogeneity. $I^2>50\%$ was considered to be an indicator of high heterogeneity. Forest plots were drawn and presented individual mechanisms of DITP as horizontal solid lines with their confidence intervals (CI). Common effect and random effect models were applied to assess the incidence of DITP, and forest plots were plotted for the case reports categorised with scores 1–3 (definite, probable, and possible association) with their 95% CIs. The random-effects model of the average weightage of studies assumes that each study provides information about a different effect size.[6]

RESULTS

The literature search yielded 1,466 case reports. After careful screening against the eligibility criteria, a total of 751 case reports were included in the meta-analysis (Figure 1). There were 380 (45.67%) males, 334 (50.6%) females, and in 28 cases (3.73%) no gender identity was revealed. There was no history of drug allergy in any case reports. The mean age of males was 55.1 years (interquartile range: 41–68; range: 2–98), and of females was 53.1 years (interquartile range: 41–68; range: 2–98).

Table 1: Percentage and number of case reports on the basis of mechanism of drug-induced thrombocytopenic purpura.

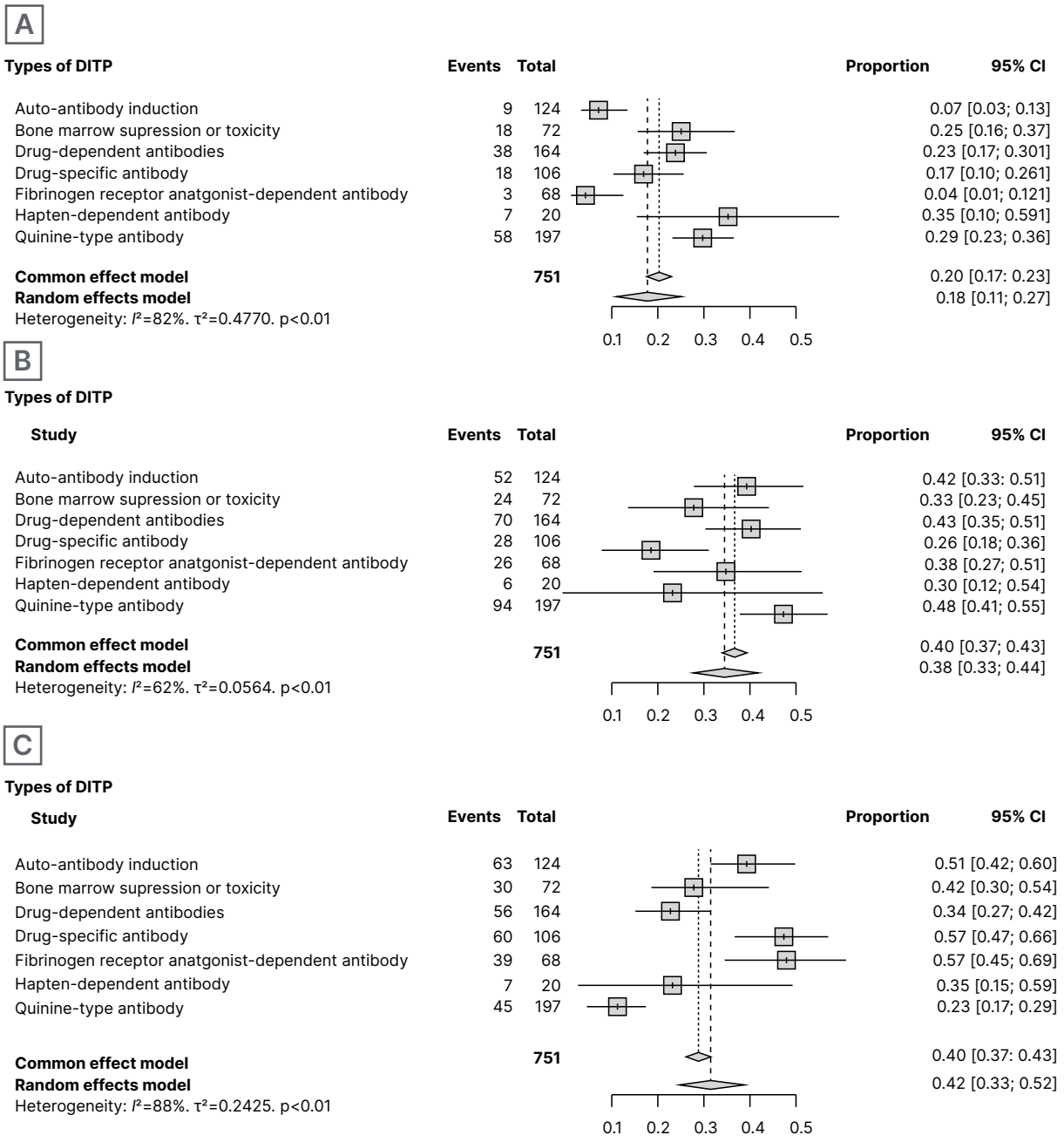
Type of drug-induced thrombocytopenia	Male, n (%)	Female, n (%)	Not available, n (%)	Median age, years (range)	Score			Total, n (%)
					1*	2†	3‡	
Drug-dependent antibodies	191 (25.3%)	163 (21.6%)	7 (0.94%)	53 (4–91)	96 (12.70%)	164 (21.84%)	101 (13.4%)	361 (48%)
Auto-antibody induction	84 (11.1%)	33 (4.39%)	7 (0.93%)	53 (6–98)	9 (1.20%)	52 (6.92%)	63 (8.39%)	124 (16.51%)
Drug-specific antibody	35 (4.66%)	64 (8.52%)	7 (0.93%)	59 (3–84)	18 (2.40%)	28 (3.73%)	60 (7.99%)	106 (14.11%)
Bone-marrow suppression or toxicity	37 (4.93%)	29 (3.86%)	6 (0.80%)	60 (3–87)	18 (2.40%)	24 (3.20%)	30 (3.99%)	72 (9.59%)
Fibrinogen receptor antagonist-dependent antibody	23 (3.06%)	45 (5.99%)	0 (0%)	51 (2–86)	3 (0.40%)	26 (3.46%)	39 (5.19%)	68 (9.05%)
Hapten-dependent antibody	10 (1.33%)	9 (1.20%)	1 (0.13%)	46 (2–82)	7 (0.93%)	6 (0.80%)	7 (0.93%)	20 (2.66%)

*Thrombocytopenia definitely caused by drug .

†Thrombocytopenia probably caused by drug.

‡Thrombocytopenia possibly caused by drug.

Figure 2: Proportion of all-article score of 1 out of total definitive incidences (A); proportion of all-article score of 2 out of total definitive incidences (B); and proportion of all articles score of 3 out of total definitive incidences (C).



CI: confidence interval; DITP: drug-induced thrombocytopenic purpura.

In 361 cases, the mechanism of DITP was drug-dependent antibodies, followed by autoantibody induction in 124 cases, drug-specific antibody in 106 cases, bone marrow suppression or toxicity in 72 cases, fibrinogen receptor antagonist-dependent antibody in 68 cases, and hapten-dependent antibody in 20 cases (Table 1).

Out of 751 articles, the score of 151 articles was 1, followed by 300 articles with a score of 2, and 300 articles with a score of 3. The incidences for all case reports score DITP by random and common effect model were 0.65% (95% CI: 0.61–0.69) and 0.65% (95% CI: 0.62–0.68) respectively.

In 151 patients with score 1, synthetic results through meta-analysis using the random and common effect models revealed an incidence of 0.16% (95% CI: 0.9–0.27) and 0.20% (95% CI: 0.17–0.23), respectively (Figure 2A). The total number of DITPs with Score 2 was reported in 300 patients, and synthetic results through meta-analysis using the random and common effect model revealed an incidence of 0.37% (95% CI: 0.31–0.44) and 0.40% (95% CI: 0.37–0.43), respectively (Figure 2B). The total number of DITPs with a score of 3 was reported in 300 patients, and synthetic results through meta-analysis using the random and common effect model revealed an incidence of 0.45% (95% CI: 0.35–0.55) and 0.40% (95% CI: 0.37–0.43), respectively (Figure 2C). Case reports of DITP scoring 4 and 5 were not included in this systematic review and meta-analysis.

In 20.8% of the case reports, antibiotics caused DITP, followed by antimalarials in 13.7%, monoclonal antibodies in 10.1%, antiplatelets in 9.0%, DMARDs in 8.16%, anti-epileptics in 6.98%, anti-cancer chemotherapeutics in 6.45%, NSAIDs in 4.61%, H2-blockers in 3.95%, antiarrhythmics in 3.82%, antipsychotics in 2.23%, diuretics in 2.10%, anti-hypertensives in 1.97%, and vaccines in 1.18%. Other miscellaneous drugs were responsible for 4.74% of DITP.

On further analysis of the incidence of DITP, the authors found that out of these 751 patients, 478 (63.6%) patients required hospitalisation. The incidence through meta-analysis was 0.64% (95% CI: 0.52–0.75) and 0.64% (95% CI: 0.60–0.67), respectively. Out of these 478 hospitalised patients, 323 (67.5%) patients had external or internal bleeding, including 120 (37.1%) with trivial bleeding, i.e., petechiae, purpura, brief epistaxis or gingival bleeding, guaiac-positive stool, or microscopic haematuria; and 141 (43.6%) patients showing minor bleeding or overt bleeding that did not meet the criteria for major bleeding (melaena, gross haematuria, epistaxis, or gingival bleeding that is prolonged for more than 30 minutes and required medical intervention; or excessive menstrual bleeding or vaginal bleeding other than menses). Further, 62 (19.1%) patients showed major bleeding intracranially or retroperitoneally, or overt bleeding, which was visible or symptomatic, with a lab-confirmed decrease in haemoglobin concentration by more than 2 g/dL, or requiring transfusion of two or more units of red blood cells. The incidence through meta-analysis was 0.62% (95% CI: 0.48–0.75) and 0.68% (95% CI: 0.63–0.72), respectively.

Additionally, a total of 12 deaths were reported, with the following medicines being identified as the cause: quinine resulted in the death of five patients; antibiotics rifampin, trimethoprim, sulfamethoxazole, and vancomycin resulted in the death of three patients; followed by oxaliplatin in two patients; eptifibatide in one patient; and phenytoin in one patient.

Through meta-analysis, the incidence was 0.03% (95% CI: 0.01–0.05) and 0.03% (95% CI: 0.01–0.04), respectively.

PUBLICATION BIAS

In this systematic review and meta-analysis, publication bias was not assessed as the case reports included were not comparable for age, sex, causative drugs, drugs classification, or relation between causative drugs and clinical subtypes.

DISCUSSION

In literature, there have been case reports or case series of DITP. To the best of the authors' knowledge, this is the first systematic review and meta-analysis to analyse DITP case reports and its mechanism.

In the present systematic review and meta-analysis, drug-dependent antibodies-induced DITP was the most frequent mechanism, which accounted for 48% of the case reports. This mechanism has been explained as an immune-mediated reaction where drug-specific antibodies are derived from pre-existing, naturally occurring antibodies in the body that have a weak affinity for platelets in the absence of causing drugs.[7] Once the sensitising drug is introduced into the body, the drug binds to platelet-specific GP IIb/IIIa or Ib/V/IX complexes. It may also interact with an intact integrin and result in conformational changes that further increase antibodies' affinity for the platelet membrane GP. The arginase 1-10 residue in the GP IX sub-unit also plays a critical role at the antigenic site.[8,9]

In this meta-analysis, quinine, quinidine, and antibiotics such as sulfamethoxazole, vancomycin, and β-lactams, anti-epileptics drugs; NSAIDs, H2-blockers, and proton-pump inhibitors were reported to cause DITP by this mechanism. The onset of drug-dependent antibodies-related manifestations approximately takes 1–2 weeks after initiation of drug therapy. However, it has been reported that antibodies often emerge over a protracted period of intermittent drug usage.[2] One retrospective analysis reported vancomycin-specific platelet-reactive antibodies in 20% (n=34) samples.[10]

Additionally, they also reported the median time to platelet nadir (mean: 13,600 per mm^3) 7 days and 93% average fall in platelet counts. Ten patients presented with severe bleeding in the form of haematuria, intrapulmonary and gastrointestinal haemorrhages, and excessive bleeding from the site of the vein punctured. During acute thrombocytopenia, 14 patients who received platelet transfusions did not show a rise in platelet counts. The sole beneficial strategy for these patients was the discontinuation of vancomycin.

In this meta-analysis, autoantibody-dependent was the second most commonly reported mechanism for DITP, which was identified in 16.5% of case reports and demonstrated by DMARDs, interferon-α procainamide, and levodopa.[11,12] The exact mechanism behind this autoantibody-mediated reaction is not understood clearly. However, laboratory and clinical data suggested that auto-antibodies are produced only in the presence of these drugs. Another proposed mechanism is an interference of the drug with platelet surface GP and the formation of unknown peptides, which further stimulate the removal of platelets by the immune system.[8]

The third reported mechanism for DITP was drug-specific antibodies, described in 14.1% of case reports. Abciximab has been reported to induce DITP in this manner. Abciximab, a chimeric (human/mouse) monoclonal antibody is used as an antiplatelet agent, and acts by binding to the anti-GP IIb/IIIa Fab fragment that blocks the binding of fibrinogen to platelet and inhibits thrombus formation.[13] After receiving abciximab, approximately 10–15% of patients may develop thrombocytopenia within 30 days due to antibody formation.[14] However, antibodies already present in blood circulation cause acute thrombocytopenia in 1–2% of patients exposed to abciximab for the first time, and 10–12% of patients treated for the second time with this drug.[9] Usually, bleeding manifestations are transient, but life-threatening intracranial haemorrhages have also been reported in many patients. IgG/IgM antibodies recognise murine sequences present in the abciximab molecule for its binding to GP IIb/IIIa, whereas non-pathogenic antibodies are specific for the papain-cleaving site of abciximab Fab fragment (not associated with platelet depletion).[12] In the authors' included case reports, most of the patients recovered within a few days, but in some patients, low platelet counts persisted for several weeks. On the other hand, delayed thrombocytopenia was also observed in a few patients after 5–10 days of treatment with abciximab, with a decrease in platelet count. This can be explained by the possibility that abciximab may be present for up to 2 weeks in circulating platelets because of the movement of the drug from one cell to another.[13] Therefore, delayed abciximab-induced thrombocytopenia could be caused by newly synthesised antibodies against the drug remaining on the surface of the platelets for an extended period. This DITP usually occurs after hospital discharge and may be severe, with a delayed diagnosis. The condition becomes more severe in patients who are on treatment with other antiplatelet drugs, such as aspirin or $P2Y_{12}$ inhibitors, favouring the occurrence of severe bleeding.[14]

The TARGET study randomised 4,809 patients and reported abciximab or tirofiban induced thrombocytopenia in 2.9% of patient undergoing percutaneous coronary intervention.[15,16] The percentage of DITP was significantly higher in abciximab in comparison to patients who received tirofiban (2.5% versus 0.5%). The study also reported lower mean nadir platelet count, higher incidence rate of profound thrombocytopenia, and longer mean days to platelet recovery in patients receiving abciximab than tirofiban. Several humanised monoclonal antibodies have also been identified as potential triggers for the formation of autoantibodies targeting platelets. Monoclonal antibodies causing DITP include efalizumab (anti-CD11a),[17,18] adalimumab,[19] infliximab (anti-TNF), bevacizumab (anti-vascular endothelial growth factor therapy),[20,21] rituximab

(anti-CD20),[22,23] natalizumab (anti-4 1-integrin),[24] and programmed death-1 or cytotoxic T-lymphocyte antigen 4.[25,26]

In the present meta-analysis, drugs causing DITP by bone marrow suppression or toxicity accounted for 9.5% of DITP cases. It is a drug-induced, non-immune mediated manner of thrombocytopenia; drugs induce myelosuppression, followed by decreased production of platelets. Oxaliplatin was the most common drug reported to cause thrombocytopenia in this manner.

Based on several reports, 45–77% of patients with colorectal cancer who received oxaliplatin developed thrombocytopenia.[1,16,27] Bleeding was not the presenting symptom in these cases, but concomitant anaemia and neutropenia were frequent. Lower mean nadir platelet is reached within 10–14 days after drug administration.[7] The other drugs reported to cause DITP by this mechanism include β-lactams, linezolid, sulphonamide, flucytosine, ganciclovir, valganciclovir, foscarnet, and albendazole.[28,29]

Fiban-type drug reaction is another mechanism of DITP (9.05%). Antiplatelet drugs eptifibatide and tirofiban, followed by vaccines, captopril, and amphotericin B were the most commonly reported drugs found to be associated with this mechanism of DITP. Ligand-mimetic fibrinogen-receptor antagonists mimic the arginine-glycine-aspartic acid sequence recognised by specific sites of the platelet GP IIb/IIIa complex. They inhibit fibrinogen-GP IIb/IIIa interactions competitively, and prevent the formation of platelet aggregates. Various studies reported tirofiban and eptifibatide as the most commonly reported compounds used to prevent thrombotic complications associated with percutaneous transluminal coronary angioplasty, and approximately 0.1–0.5% of patients may develop thrombocytopenia when treated first with these drugs. This adverse event was reported to develop in some patients within the first 24 hours of treatment, with clinical complaints of fever, chills, and hypotension.[30] However, most of the patients recovered within a few days without severe bleeding.

Platelet-sensitive antibodies recognise a neoepitope or a ligand-induced binding site expressed by GP IIb/IIIa to cause platelet destruction.[29] Eptifibatide-dependent antibodies do not bind to GP IIb/IIIa in the presence of tirofiban, and vice versa.

These antibodies may be present naturally without any previous history of drug exposure.[31,32]

Hapten-dependent antibodies mechanism of DITP is 2.66%. Haptens are small molecules and are themselves not immunogenic, but once they bind covalently to macromolecules like proteins, they synthesise drug-specific antibodies against platelets. This mechanism was reported with penicillin and cephalosporin drugs, which may bind to red blood cells via their β-lactam ring, and induce immune haemolytic anaemia. Another mechanism for immune-mediated thrombocytopenia may be the covalent binding of penicillin or their derivatives with platelet GPs and induction of antibody response.[33-35] Cephalosporins (mainly ceftriaxone) have been reported to cause DITP, with antibodies recognising GP IIb/IIIa or GP Ib/IX, especially the GP IX sub-unit.[36]

The overall mortality of patients with DITP was 1.5% in the meta-analysis. Death rate with drug-dependent antibodies type appeared to be higher in quinine recipients. Allergic reactions to quinine can be severe, and can cause severe multi-organ failure. Early recognition is critical for the prevention of recurrent episodes.

CONCLUSION

In this systematic review and meta-analysis, the authors found that antibiotics, antimalarials, monoclonal antibodies, antiplatelets, DMARDs, anti-epileptics, and anti-cancer chemotherapeutic drugs were commonly associated with DITP. Clinicians should be aware of the potential of drugs causing DITP as an adverse event, which may affect patient compliance and adherence to drugs. Unrecognised DITP may also lead to severe thrombocytopenia and inappropriate patient management.

References

1. Bakchoul T, Marini I. Drug-associated thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2018;2018(1):576-83.
2. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med. 2007;357(6):580-7.
3. George JN et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med. 1998;129(11): 886-90.
4. Priziola JL et al. Drug-induced thrombocytopenia in critically ill patients. Crit Care Med. 2010;38(Suppl 6):S145-54.
5. Page MJ et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
6. Han B, Eskin E. Random-effects model aimed at discovering associations in meta-analysis of genome-wide association studies. Am J Hum Genet. 2011;88(5): 586-98.
7. Jardim DL et al. Oxaliplatin-related thrombocytopenia. Ann Oncol. 2012;23(8):1937-42.
8. Asvadi P et al. Drug-induced thrombocytopenia: localization of the binding site of GPIX-specific quinine-dependent antibodies. Blood. 2003;102(5):1670-7.
9. Aster RH et al. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost. 2009;7(6):911-8.
10. Von Drygalski A et al. Vancomycin-induced immune thrombocytopenia. N Engl J Med. 2007;356(9):904-10.
11. Landrum EM et al. Prolonged thrombocytopenia associated with procainamide in an elderly patient. Ann Pharmacother. 1994;28(10):1172-6.
12. Giner V et al. Thrombocytopenia associated with levodopa treatment. Arch Intern Med. 2003;163(6):735-6.
13. Coller BS. Platelet GPIIb/IIIa antagonists: the first anti-integrin receptor therapeutics. J Clin Invest. 1997;100(Suppl 11):S57-60.
14. Curtis BR et al. Delayed thrombocytopenia after treatment with abciximab: a distinct clinical entity associated with the immune response to the drug. J Thromb Haemost. 2004;2(6):985-92.
15. Mascelli MA et al. Pharmacodynamic profile of short-term abciximab treatment demonstrates prolonged platelet inhibition with gradual recovery from GP IIb/IIIa receptor blockade. Circulation. 1998;97(17):1680-8.
16. Merlini PA et al. Thrombocytopenia caused by abciximab or tirofiban and its association with clinical outcome in patients undergoing coronary stenting. Circulation. 2004;109(18):2203-6.
17. Kiorpelidou D et al. Efalizumab-induced thrombocytopenia: report of relapse after re-administration. Clin Exp Dermatol. 2009;34(8):e914-6.
18. Warkentin TE, Kwon P. Immune thrombocytopenia associated with efalizumab therapy for psoriasis. Ann Intern Med. 2005;143(10): 761-3.
19. Casanova MJ et al. Severe adalimumab-induced thrombocytopenia in a patient with Crohn's disease. J Crohns Colitis. 2012;6(10):1034-7.
20. Kumar J et al. Bevacizumab-induced reversible thrombocytopenia in a patient with adenocarcinoma of colon: rare adverse effect of bevacizumab. Case Rep Oncol Med. 2012;2012:695430.
21. Dior M et al. A rare hematological adverse event induced by bevacizumab: severe thrombocytopenia. Am J Med. 2012;125(8):828-30.
22. Yi JH et al. Rituximab-induced acute thrombocytopenia: a case report and review of the literature. Med Oncol. 2009;26(1):45-8.
23. Omura Y et al. Rituximab-induced acute thrombocytopenia in a patient with follicular lymphoma: a case report and review of the literature. Intern Med. 2018;57(8):1151-4.
24. Cachia D et al. Drug-induced thrombocytopenia secondary to natalizumab treatment. BMJ Case Rep. 2014;2014:bcr2013203313.
25. Shiuan E et al. Thrombocytopenia in patients with melanoma receiving immune checkpoint inhibitor therapy. J Immunother Cancer. 2017;5:8.
26. Ahmad S et al. Ipilimumab-induced thrombocytopenia in a patient with metastatic melanoma. J Oncol Pharm Pract. 2012;18(2):287-92.
27. Patel N et al. A comparative evaluation of adverse platelet outcomes among Veterans' Affairs patients receiving linezolid or vancomycin. J Antimicrob Chemother. 2012;67(3):727-35.
28. Bernstein WB et al. Mechanisms for linezolid-induced anemia and thrombocytopenia. Ann Pharmacother. 2003;37(4):517-20.
29. Kumar A et al. Piperacillin induced bone marrow suppression: a case report. BMC Clin Pharmacol. 2003;3:2.
30. Gao C et al. Eptifibatide-induced thrombocytopenia and thrombosis in humans require FcgammaRIIa and the integrin beta3 cytoplasmic domain. J Clin Invest. 2009;119(3):504-11.
31. Bougie DW et al. Antibodies causing thrombocytopenia in patients treated with RGD-mimetic platelet inhibitors recognize ligand-specific conformers of αIIb/β3 integrin. Blood. 2012;119(26):6317-25.
32. Billheimer JT et al. Evidence that thrombocytopenia observed in humans treated with orally bioavailable glycoprotein IIb/IIIa antagonists is immune mediated. Blood. 2002;99(10):3540-6.
33. Salamon DJ et al. Red cell and platelet-bound IgG penicillin antibodies in a patient with thrombocytopenia. Transfusion. 1984;24(5):395-8.
34. Murphy MF et al. Demonstration of an immune-mediated mechanism of penicillin-induced neutropenia and thrombocytopenia. Br J Haematol. 1983;55(1):155-60.
35. Lang R et al. Adverse reactions to prolonged treatment with high doses of carbenicillin and ureidopenicillins. Rev Infect Dis. 1991;13(1):68-72.
36. Grossjohann B et al. Ceftriaxone causes drug-induced immune thrombocytopenia and hemolyticanemia: characterization of targets on platelets and red blood cells. Transfusion. 2004;44(7):1033-40.

Post-SARS-CoV-2 Multisystemic Syndrome in the Paediatric Population of Pakistan: A Case Report

Authors: *Fazeela Bibi, Fatima Nayyer, Maham Zehra, Sara Jabeen

Jinnah Medical and Dental College, Karachi, Pakistan
*Correspondence to fazeelabibi@hotmail.com

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Abstract

A rare life-threatening condition has been noticed in children who have been previously infected with COVID-19, involving organ inflammation, named as a multisystem inflammatory syndrome. In this study, the authors analyse a unique case, describe possibilities of disease manifestation in a particular individual, and detail different treatment options. Along with treatment and monitoring, all eligible children should be vaccinated against COVID-19. Unfortunately, due to decreased availability and increasing demand for the COVID-19 vaccine, the government in Pakistan has been led to vaccinate the general population on the basis of age group. Currently, individuals older than 12-years-old are being vaccinated, but not those who are younger. As a result, younger children have a higher chance of being infected with COVID-19 and developing multisystem inflammatory syndrome in children (MIS-C). Vaccination against the virus reduces the likelihood of COVID-19 infection. MIS-C is a rare condition found in children that might be fatal, and current evidence indicates that MIS-C occurs due to exaggerated immune response.

Key Points

1. Every paediatrician should have basic knowledge about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its related complications, as well as all aspects of the disease. Paediatricians should listen to their patient's concerns, and provide best possible care in accordance with latest medical research and best practices.

2. This article presents a unique case of multisystemic inflammatory syndrome in children (MIS-C) secondary to SARS-CoV-2 and details the clinical manifestation of the illness, investigations, and management. It emphasises that healthcare professionals should investigate for the presence of multiple organ system manifestation. MIS-C is a potential diagnosis for every patient presenting with fever, rash, and systemic manifestations, along with Kawasaki disease and other illnesses.

3. MIS-C is a rare but life-threatening complication of SARS-CoV-2, with children being the most impacted by the disease. As a result of young children not being vaccinated against COVID-19, MIS-C has become a leading concern. This study aims to provide valuable information about the disease and its prevention from complications.

INTRODUCTION

A novel characterised hyper inflammatory condition has been observed in children who have recently had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections during the COVID-19 pandemic. Children with this condition had fever and general sickness, as well as occasionally shock, cardiac involvement, and multiple organ failure. After being discovered in the UK, reports of this ailment later spread to other regions of Europe and the USA.[1-3] A study conducted in the UK showed a remarkable number of hospitalised patients who became extremely ill, and developed acute respiratory distress syndrome and multiple organ failure as a result of COVID-19. Multiple organ dysfunction might involve multiple organ systems.

A 61% increase in mortality rate was seen post-kidney failure in approximately half of the patients who developed acute respiratory distress syndrome after contracting COVID-19.[4] Serious illness has been reported in children with the new syndrome, which occurred after COVID-19 infection, with clinical presentations resembling to that of Kawasaki disease and toxic shock syndrome.[5] SARS-CoV-2 causes deregulated immune response that snuffs out antibodies and causes a drastic decrease in functional capacity, leading to insistent extrapulmonary infection.[6]

A study conducted in North America revealed that 45 patients of the paediatric age group (median age: 9) were admitted to hospital as a result of MIS-C. Cardiac involvement was apparent in nearly 80% of children, which involved coronary artery dilatation and reduced cardiac output. Most patients had raised levels of inflammatory markers, as well as raised cardiac biomarkers that suggested cardiac injury. Patients were managed with immunoglobulins, corticosteroids, and immune modulators to reduce the inflammatory reaction. One-third of the patients were treated with non-invasive breathing assistance; however, none of the patients required support from a ventilator. In addition, more than half of the patients were treated for low blood pressure. Furthermore, it was observed in the following study that the inflammatory markers and cardiac biomarkers had returned to its normal range tertian. Cardiac abnormalities, as well as coronary artery dilation, was not seen in patients after 4 months.[7]

CASE REPORT

A 9-year-old, previously healthy, female child presented in the Holy Family hospital, Karachi, Pakistan, in the outpatient department in September 2020, presenting with fever, abdominal pain, and vomiting for 2 weeks. The fever was sudden in onset, intermittent, and documented up to 103 °F; it was not associated with rigors and chill. Abdominal pain was generalised, episodic, and moderate in intensity; there were no aggravating or relieving factors. Vomiting accompanied the pain and was non-projectile. The patient had two episodes a day that contained food particles and it was not associated with bleeding. There was no history of earlier hospital admissions. The child lived in a home with four other family members, and there was no history of travel or contact with sick individuals. There were no known allergies. The patient took syrup acetaminophen to treat their symptoms.

On admission, the patient's vitals were temperature: 101 °F; blood pressure: 97/63 mmHg; pulse: 100 bpm; respiratory rate: 20 bpm; saturation of peripheral O_2: 96% at room air; and weight: 29 kg. The patient was alert and oriented with time place and person. Their Glasgow Coma Scale (GCS) was 15/15. Physical examination revealed generalised maculopapular rash all over their body, oral ulcers, and conjunctivitis. Pallor, cyanosis, clubbing, oedema, icterus, and lymphadenopathy were absent. The rest of the systemic examination was unremarkable; however, on cardiovascular examination, gallop sounds were observed while the respiratory system had no significant finding.

There was no visceromegaly or tenderness present upon abdominal examination.

The patient was febrile on arrival, and intravenous paracetamol 1 g was given for fever. A broad-spectrum antibiotic, ceftriaxone, was given, with the dose of 1.5 g once daily. Intravenous fluid of half-strength dextrose saline was given as maintenance fluid.

Laboratory investigations were done, including baseline investigations, dengue antibodies, malarial parasite, urine detailed report, and blood cultures. The complete blood count revealed haemoglobin of 10.8 g per decilitre (10.9–14.9 g/dL), total leukocytes count of 18.1×10^9/L ($4.5–14.5\times10^9$/L), neutrophils of 93% (38–68%), and lymphocytes of 5% (25–54% [Table 1]).[8]

Dengue antibodies and malaria parasite were negative. The urine report was insignificant. The initial blood culture and sensitivity was negative at 48 hours. The child had a recurrent fever spike of up to 102 °F. On the third day of admission, reverse transcription PCR and antibodies were sent to rule out the cause of underlying fever. The reports were PCR negative, and SARS-CoV-2 antibodies IgM and IgG were reactive.

Conclusion

Biventricular dysfunction; moderate to severe left ventricular systolic dysfunction; and ejection fraction of 30–35% inflammatory markers, including C reactive protein, erythrocyte sedimentary rate, D-dimer, lactate dehydrogenase, and ferritin were sent, revealing C-reactive protein of 192 mg/L (normal value: <10 mg/L), erythrocyte sedimentation rate of 70 mm/hour (normal value: ≤10 mm/hour) and D-dimer of 4.99 µg fibrinogen equivalent units/mL (normal value: <0.5 µg fibrinogen equivalent units/mL), while ferritin was 876 ng/mL (normal range: 20–200 ng/mL) and lactate dehydrogenase reported as 466 U/L (normal range: 240–480 U/L). Chest X-ray reports were unremarkable. Echocardiography revealed biventricular dysfunction, moderate to severe generalised left ventricular dysfunction, and ejection fraction of 35 percent. The patient was diagnosed with multisystemic inflammatory syndrome.

The patient was started on an injection of methylprednisolone (dose: 500 mg once daily for 5 days). Tablet aspirin (60 mg) was given once daily for venous thromboembolism prophylaxis, while tablet captopril (8 mg) and tablet furosemide (5 mg) were prescribed for three times a day for left ventricular dysfunction and reduced ejection fraction.

The patient was afebrile since the fifth day after admission, and was vitally stable. The patient was discharged on the sixth day after admission. They were discharged on oral antibiotic syrup cefixime (5 mL/200 mg) once daily for prophylaxis of bacterial infection, as the final blood culture report was still pending, and had to be reported 7 days after collecting the blood culture. Tablet prednisolone was prescribed (one tablet, three times a day). The authors continued to prescribe aspirin and captopril on discharge at the same dosage. The patient was advised for follow-up in 3 days, with the final blood culture report. The final blood culture came back as negative, after which the patient was no longer prescribed with antibiotics. See Table 2 and Figure 1 for the patient's clinical course.

DISCUSSION

MIS-C is a rare, fatal syndrome that affects individuals who have been infected with COVID-19. The authors' case report highlights a patient who had no history of illness with prior SARS-CoV-2 infection, and then developing multisystemic inflammatory syndrome. Currently, evidence indicates that MIS-C occurs due to hyperbolic immune response, initiated by prior COVID-19 infection.[9] In SARS-CoV-2, cellular entry occurs when viral proteins interact with multiple angiotensin-converting enzyme receptors represented by multiple organ system.[10]

Furthermore, the Centers for Disease Control and Prevention (CDC) defined MIS-C in five points. The first point was if an individual less than 21-years-old and presents with fever; second point mentions importance of diagnostic markers in making diagnosis, including C-reactive protein, fibrinogen, and erythrocyte sedimentation rate, which are markers of inflammation; the third point highlights clinical symptoms exhibition, critical ailment needing hospitalisation, and

Table 1: Clinical data.[8]

Parameters	Result values	Normal reference range values	Conventional units
Haemoglobin	10.8	10.9–14.9	g/dL
Total leukocyte count	18.1	4.5–14.5	x10^9 /L
Neutrophils	93%	38–68%	N/A
Lymphocyte	5%	25–54%	N/A
ESR	70	<10	mm/hour
C-reactive protein	192	<10	mg/l
D-dimers	4.99	<0.5	µg FEU/mL
Ferritin	876	20–200	ng/mL
LDH	466	240–480	U/l
Dengue antibodies	Negative	Negative	N/A
Malaria parasite	Negative	Negative	N/A
RT-PCR	Non-reactive	Non-reactive	N/A
SARS-CoV-2 (IgM) antibody	Positive	Negative	N/A
SARS-CoV-2 (IgG) antibody	Positive	Negative	N/A
Echocardiogram			
Structural interpretation	Doppler study: colour Doppler	Pulmonary artery systolic pressure	
Moderate to severe left ventricle systolic dysfunction	Tricuspid regurgitation (mild)	15 mmHg (normal range: <25 mmHg)	
Normal size left atrium	Mitral regurgitation (mild)	N/A	
Normal size right atria and right ventricle with depressed function	N/A	N/A	

ESR: erythrocyte sedimentation rate; FEU: fibrinogen equivalent unit; LDH: lactate dehydrogenase; N/A: not applicable; RT-PCR: reverse transcription-PCR; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

more than two organ systems entailment (cardiovascular, renal, respiratory, haematological, gastrointestinal, mucocutaneous, or neurological); the fourth point states that there should be no other alternative diagnosis; and the fifth point highlights that requirement of confirmed reverse transcription-PCR serology, antigen testing, or negative SARS CoV-2 test but exposure to a suspected or confirmed COVID-19 case within 4 weeks prior to onset of symptoms.[1]

Table 2: Clinical course.

Day of admission	Clinical event
Day 1	Admitted to paediatric ward. Patient was febrile on arrival Investigations sent (CBC, MP, dengue serology, urine DR, blood C/S) Initially treated with IV ceftriaxone and paracetamol
Day 3	Initial blood C/S after 48 hours was negative Fever spike of 101 °F Inflammatory markers, COVID-19 serology, and PCR sent under suspicion of MIS-C PCR negative, COVID-19 serology IgM and IgG positive, and raised levels of inflammatory markers Echocardiogram: biventricular dysfunction and LV dysfunction; EF: 35% Diagnosed with multisystem inflammatory syndrome Methylprednisolone, aspirin captopril, and furosemide Antibiotics continued until final culture report (7 days)
Day 5	Fever vanished No complaint of abdominal pain Rashes began to subside Oral intake improved
Day 6	Patient discharged on tablet aspirin, prednisolone, and captopril Oral antibiotic syrup cefixime given while waiting for the final blood C/S reports Advised to follow-up in 3 days with culture report

CBC: complete blood count; C/S: culture and sensitivity; DR: detailed report; EF: ejection fraction; IV: intravenous; LV: left ventricular; MIS-C: multisystem inflammatory syndrome in children; MP: malaria parasite.

The authors' patient met the requirement bestowed in the case definition. There was history of fever, elevation of inflammatory markers, cardiac, gastrointestinal and mucocutaneous involvement, and positive SARS-CoV-2 serology. A study reveals that gastrointestinal involvement is the most common clinical manifestation in MIS-C, followed by cardiac manifestation, in the paediatric population.[11]

Maculopapular rash with fever can be brought on by a broad variety of illnesses, such as roseola, which causes high-grade fever, cough, coryza, and conjunctivitis, along with Koplik's spot on buccal mucosa. Moreover, rubella, which shows painful adenopathy in the posterior auricular and posterior cervical lymph nodes, and relates to petechiae on the soft palate, is another infectious condition that may present with rash and fever. Additionally, Kawasaki disease also presents with diffuse rash, which spares the face but does have conjunctivitis of both eyes; cervical lymph nodes involvement may also be seen. Lastly, a patient with Kawasaki disease could have strawberry tongue on oral examination. Furthermore, scarlet fever manifests as a rash that spares the face, palms, and soles of the feet. This condition also has a quick onset of a fever, lethargy, pharyngitis, and strawberry tongue. Lastly, some medications might cause maculopapular rash, which commonly appears 4–21 days after starting a new medication; the rash may also rapidly spread and be diffuse in character.

In the authors' patient, there was a diffuse rash that covered the entire body, which was

Figure 1: Clinical course of a patient with multisystemic inflammatory syndrome in children.

CBC: complete blood count; C/S: culture and sensitivity; IV: intravenous; MIS-C: multisystem inflammatory syndrome in children; MP: malaria parasite; Temp.: temperature; UDR: urine detailed report.

accompanied by a high-grade fever, but there was no pharyngitis, tonsillitis, or adenopathy. There were no findings on oral examination other than oral ulcers, and there was no history of starting any new medications, as per the CDC guidelines, as a result of multiple organ involvement, along with maculopapular rash, it was possible that the rash was caused by MIS-C.[12]

In the middle of 2020, the first case of MIS-C was reported in UK. The patient's symptoms were a similar presentation of atypical Kawasaki and toxic shock syndrome, which was a manifestation of severe COVID-19.[13] Kawasaki disease presents with acute inflammation of medium sized vessels in paediatric population under 5-years-old, and typically occurs between the ages of 9–11 months.[14]

Though the cause of Kawasaki disease remains unknown, the clinical presentation of COVID-19 illness resembles that of Kawasaki disease, occurring after an infection that leads to a cascade of inflammatory events,[15] and leads to symptoms involving the gastrointestinal system. For instance, abdominal pain, reduced oral intake, and vomiting are more common in MIS-C compared with Kawasaki disease.[16] Kawasaki disease and MIS-C have some factors in common, including prolonged history of fever, rash, oral mucositis, conjunctivitis, and raised inflammatory markers, as seen in the authors' patient's case. However, in 75% of the cases, Kawasaki disease involves a younger paediatric population, typically less than 5 years old; abdominal symptoms are less frequent; and multiple organ dysfunction is rare. Ventricular dysfunction is reported in acute cases of Kawasaki disease. In the authors' case, the patient presented with left ventricular dysfunction, which is not typically seen in acute phases of Kawasaki disease. The child also had gastrointestinal symptoms, such as abdominal pain, whereas gastrointestinal symptoms are only present in 20% of the cases in Kawasaki disease.[17]

A previous cohort study conducted on children who tested positive with SARS-CoV-2 showed cardiac involvement in 13 out of 2,135 patients.[18] A 2020 study also showed that patients with COVID-19 had a 16% advanced risk myocarditis compared with individuals who were not infected. Children under the age of 16 who were infected are at a 37-times higher risk of developing myocarditis, while the 16–39 age group are at a 7-times higher risk compared with individuals who are not infected with COVID-18.[19]

A large cohort study showed that individuals with MIS-C usually presented with tachycardia, and occasionally with hypotension, which led to increased mortality rate. This study also highlighted that 7% of cases resulted in decreased cardiac output because of left ventricular systolic and diastolic dysfunction. Furthermore, left ventricular diastolic dysfunction was also found in more than half of individuals.[20] Another prospective case study conducted in France observed ejection fraction of as low as 10%.[21] This suggests that myocardial dysfunction related to SARS-CoV-2 does not just affect children, but also adolescents and adults, making it a wide range viral infection. A study conducted in the UK and Italy highlighted important laboratory findings, suggestive of MIS-C with neutropenia, lymphopenia, thrombocytopenia, and elevated inflammatory markers, with raised levels of serum triglycerides, ferritin, and D-dimer. COVID-19 infection was not identified in a couple of patients following SARS-CoV-2 PCR, serology, and antigen testing.[1,22]

Managing MIS-C is similar to that of Kawasaki disease. The patients who present with mild symptoms in MIS-C are managed with an intravenous immunoglobulin infusion 2 g/kg, and the dose is repeated if there is resistance. The addition of other drugs, such as corticosteroids, cyclosporine, and biological agents (e.g., anti-IL-1) can reduce the risk cardiac manifestations such as coronary artery dilation.[23] Patients with moderate to severe illness are treated with intravenous immunoglobulins, aspirin, and methylprednisolone. For those with moderate illness, the dose is 10–20 mg/kg/day for 1–3 days, followed by a maintenance dose; meanwhile, 30 mg/kg/day methylprednisolone is given to patients with severe disease for 3 days as a pulse therapy. Patients who have no response to two doses of intravenous immunoglobulins and steroids are managed with biological agents, such as anti-TNF and anti-IL-1. Although the role of anticoagulants in not well explained, enoxaparin can be given for thromboprophylaxis in MIS-C.[16] Patients with MIS-C reported earlier were mostly managed in intensive care, and have been treated with intravenous immunoglobulins, steroids, TNF-α inhibitor.[24]

The patient in the authors' case report recovered with supportive care and without being admitted to the intensive care unit. There was prompt improvement in patient's condition after administrating steroids and anticoagulants, without being treated with immunoglobulins.

The incidence of COVID-19 is on the rise. Every child that presents with prolonged fever should be carefully assessed for multiple organ system manifestation, and should be carefully monitored in hospital. Empirical antibiotics were initially started, as clinical signs and symptoms of MIS-C resemble to that of other serious bacterial infections.[25] Supportive care should be given. The CDC has recommended vaccination for children aged 6 months and older,[26] as per the recommendations. Unfortunately, due to the decrease in availability and increasing demand of COVID-19 vaccine in Pakistan has led the government to vaccinate the general population on basis of age.[27]

On 28th September 2021, the National Command and Operation Center (NCOC) decided to start vaccinating children aged 12 and above, but not children below this age. This is the reason why younger children might be at a higher risk of becoming infected with COVID-19 and developing MIS-C, compared with adults.[28]

CONCLUSION

The incidence of COVID-19 on the rise, and every child who presents with prolonged fever should be carefully assessed for multiple organ system manifestation, and should be carefully monitored in hospital. Empirical antibiotics should be started, and supportive care should be given. MIS-C is a rare condition that can present with mild to severe illness. Most children improve clinically with medical care, while others rapidly deteriorate. Hence, the COVID-19 vaccine should be encouraged in the paediatric population falling in this age group, as recommended by CDC guidelines. The vaccine reduces the probability of contracting COVID-19; thereby reducing the risk of MIS-C.

References

1. Riphagen S et al. Hyperinflamatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607-8.
2. Hernández C et al. Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain. Pediatr Infect Dis J. 2020;39(8):e195-8.
3. Imperial College London. Mechanisms of multiorgan failure in COVID-19. NCT04399603. https://clinicaltrials.gov/ct2/show/NCT04399603.
4. Ajmi H et al. A fatal toxic shock-like syndrome post COVID-19 infection in a child. Riv Ital Pediatr. 2021;47(1):120.
5. Patel P et al. Clinical characteristics of multisystem inflammatory syndrome in adults: a systemic review. JAMA Netw Open. 2021;4(9):e2126456.
6. Farooqi K et al. Longitudinal outcomes for multisystem inflammatory syndrome in children. Pediatrics. 2021;148(2):e2021051155.
7. Simpson J, Newburger J. Multisystem inflammatory syndrome in children in association with COVID-19. 2020;142(5): 437-40.
8. Mayo Medical Laboratories. Complete blood count normal pediatric values. Available at: http://a1.mayomedicallaboratories.com/webjc/attachments/110/30a2131-complete-blood-count-normal-pediatric-values.pdf. Last accessed: 12 June 2023.
9. Coperchin F et al. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020;53:25-32.
10. Centers for Disease Control and Prevention (CDC). Symptoms of COVID-19. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Last accessed: 15 December 2021.
11. Muzamdar S et al. The rash with maculopapules and fever in children. Clin Dermatol. 2019;37(2):119-28.
12. World Health Organization (WHO). Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020. Available at: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Last accessed: 17 December 2021.
13. Kawasaki T et al. A new infantile muco-cutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54(3): 271-6.
14. Rowley AH et al. Kawasaki disease an infectious disorder? Int J Rheum Dis. 2018;21(1):20-5.
15. Carraro M et al. Case report: multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 with coronary involvement. Arch Clin Biomed Res. 2020;4(6)760-65.
16. Radia T et al. Multisystem inflammatory syndrome in children and adolescents (MISC): a systemic review of clinical features and presentation. Peadiatr Respir Rev. 2021;38:51-7.

17. Dong Y et al. Epidemiology of COVID-19 among children in China. J Am Acad Child Adolesc Psychiatry. 2020;145(6):e20200702.

18. Jenco M. Myocarditis risk 37 times high for children with COVID-19 than infected peers. 2021. Available at: https://publications.aap.org/aapnews/news/16388/Study-Myocarditis-risk-37-times-higher-for?autologincheck=redirected. Last accessed: 17 December 2021.

19. Xu et al. Clinical characteristics and risk factors of cardiac involvement in COVID-19. J Am Heart Assoc. 2020;9(18):e016807.

20. Toubiana J et al. Kawasaki-like multisystem inflammatory syndrome in children during covid-19 pandemic in Paris; France: prospective observational study. BMJ. 2020;369:m2094.

21. Verdoni L et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771-8.

22. Kobayashi T et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet. 2012;379(9826):1613-20.

23. Ramcharan T et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. Pediatric Cardiol. 2020;41(7): 1391-401.

24. Toczyłowski K et al. Use of broad-spectrum antibiotics in children diagnosed with multisystem inflammatory syndrome temporarily associated with SARS-CoV-2 infection in Poland: the MOIS-CoR study. Int J Infect Dis. 2022;122:703–9.

25. Centers for Disease Control and Prevention (CDC). Stay up to date with vaccines. 2019. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html. Last accessed: 12 June 2023.

26. Sick-Samuels AC, Messina A. COVID vaccine: what parents need to know. 2021. Available at: https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/covid19-vaccine-what-parents-need-to-know. Last accessed: 17 December 2021.

27. DAWN News. NCOC decides to start vaccinating childrens aged 12 and above. 2021. Available at: https://www-dawn-com.cdn.ampproject.org/v/s/www.dawn.com/news/amp/1648933?usqp=mq331AQKKAFQArABIIACAw%3D%3D&amp_js_v=a6&amp_gsa=1#referrer=https%3A%2F%2Fwww.google.com&csi=1&ampshare=https%3A%2F%2Fwww.dawn.com%2Fnews%2F1648933. Last accessed: 17 December 2021.

IL-17 and -23 Inhibitors for the Treatment of Psoriasis

Authors: *Sonali Batta,[1] Ramlah Khan,[1] Marcus Zaayman,[2] Allison Limmer,[2] Dario Kivelevitch,[1,2] Alan Menter[1,2]

1. College of Medicine, Texas A&M University, Dallas, USA
2. Division of Dermatology, Baylor Scott & White Health, Dallas, Texas, USA

*Correspondence to sonalibatta@tamu.edu

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Abstract

Psoriasis is a chronic inflammatory skin condition with a significant global burden of disease and a wide array of potential treatment options, ranging from topical to systemic therapies. There are currently 11 biologic agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate-to-severe psoriasis. The emergence of IL-17 and IL-23 inhibitors has significantly improved the efficacy and safety of treatment options for patients with psoriasis. Given the number of potential therapies, a variety of factors may be considered in optimising a patient's regimen, including efficacy, safety, cost, persistence rate, and discontinuation rate. The aim of this narrative review is to provide a concise yet comprehensive review of the biologic agents that inhibit IL-17 or IL-23 available for patients 18 years of age or older with moderate-to-severe psoriasis.

Key Points

1. Psoriasis is a chronic and debilitating dermatologic condition with significant global burden of disease. Given the arsenal of newer biologics available for treatment of moderate-to-severe plaque psoriasis, there is a need for a condensed review of these medications that incorporates not only data on efficacy and side effects, but also elements of the patient experience.

2. This manuscript provides a comprehensive and holistic, yet concise, analysis of these biologics, and is designed to serve as a useful reference for clinicians when deciding how to best optimise the management of psoriasis for each patient.

3. The newer biologics available for treatment of moderate-to-severe plaque psoriasis in adults have shown clear superiority in many metrics to older treatment options. Determining the optimal biologic of choice for each patient requires consideration of factors such as patient preference and goals, safety, cost, long-term efficacy, rapidity of response, comorbidities, biologic naivety, and the unique features of each biologic.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder affecting approximately 60 million people worldwide.[1] The condition presents with rapid hyperproliferation and dysregulated differentiation of epidermal keratinocytes, manifesting clinically as salmon pink plaques with overlying silvery-white scale.[2] Mild disease is often treated topically, while moderate-to-severe cases require systemic therapy. The advent of biologic agents has significantly improved treatment outcomes and provided more favourable safety profiles than traditional immunosuppressive therapies, such as methotrexate.[3] Biologic agents modulate cytokine activity implicated in the pathogenesis of psoriasis.[3] IL-23 is a cytokine involved in the immune response to bacterial and fungal infections.[2] Dysregulation of IL-23 production may result in autoimmune inflammation.[2] The IL-23 complex is also an upstream regulatory cytokine that impacts proliferation of T helper 17 cells, which secrete cytokines such as IL-17, IL-22, and TNF-α.[2,3] These inflammatory mediators provide targets that can be intervened upon with biologic agents.

There are currently eleven biologic medications approved by the U.S. Food and Drug Administration (FDA) for treatment of moderate-to-severe psoriasis.[3] Given the multitude of treatment options, a host of factors must be considered when choosing the best regimen.[4–7] Of these, adherence, patient satisfaction, and preference are significant and heavily interlaced.[6,8,9] Medication adherence is the degree to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider.[4,10] Patient preferences and satisfaction play a key role in medication adherence, and should be taken into account so the goals and perceptions of both the patient and physician are in alignment.[6,8,11,12] These variables can be quantified using surrogate measures such as efficacy, safety, cost, persistence rate, and discontinuation rate.[4] The Psoriasis Area and Severity Index (PASI) score is used to quantify the severity of psoriasis by rating three variables (erythema, induration, and scale of psoriatic plaques) to produce a score ranging from 0 to 72.[13] Mild-to-moderate psoriasis has a PASI score of ≤10, while severe psoriasis has a score of >10.[13] Nowadays, the FDA and clinical trials use a reduction of ≥75% of PASI, termed PASI75, as an endpoint to assess the efficacy of psoriasis therapies.[14] However, the severity of psoriasis is not a reliable measure of the psychological impact of disease on health-related quality of life (QoL).[15] Therefore, patient-reported outcomes are a critical component of treatment evaluation.[15]

In the past decade, with the advent of IL-17 and IL-23 inhibitors, the improvement in efficacy and safety have provided an unprecedented change in the management of psoriasis. Indeed, although several clinical trials have demonstrated the improved profiles of these biologics, real-life data are important because these refer to patients who are typically excluded by clinical trials.[16] Rigid inclusion and exclusion criteria of clinical trials frequently exclude patients with several comorbidities, with other forms than plaque psoriasis, and with ongoing concomitant medications such as elderly patients.[17,18] This review provides a concise yet thorough reference of the biologic agents that inhibit IL-17 or IL-23 available for patients aged 18 years or older with moderate-to-severe psoriasis. Additionally, while there are further biologic and non-biologic treatment options for psoriatic arthritis, the authors only discuss psoriatic arthritis therapy in the context of agents appropriate for treatment of plaque psoriasis.

REVIEW

IL-17 Inhibitors

Secukinumab

Secukinumab is a fully humanised IgG1κ monoclonal antibody that selectively inhibits IL-17A.[3] Initial dosing is 300 mg, administered subcutaneously (SQ) at Weeks 0, 1, 2, 3, and 4, followed by 300 mg SQ maintenance dosing every 4 weeks.[3] For those patients with a lower total body weight and/or decreased severity of psoriasis, 150 mg every 4 weeks may be a suitable alternative maintenance dose.[3] Conversely, patients with a more resistant form of disease and/or a higher total body weight may benefit from a more aggressive maintenance regimen of 300 mg SQ every 2 weeks.[3]

In terms of efficacy, in the ERASURE and FIXTURE randomised controlled trials (RCT), secukinumab had a PASI75 rate of 82% and PASI90 of 59%.[19] It is effective in treatment of plaque psoriasis and difficult to treat clinical manifestations such as scalp psoriasis, nail psoriasis, and palmoplantar psoriasis.[3] In a recent real-life monocentric cohort study, secukinumab showed considerable efficacy in treatment of erythrodermic psoriasis and sustained drug survival through Week 48 of treatment.[20] Secukinumab has also demonstrated high satisfaction and perceived improvement by users.[12]

Additionally, it is effective in the treatment of psoriatic arthritis.[3,5]

Secukinumab has a very high recapture rate; after cessation of treatment and subsequent exacerbation of psoriasis, resuming secukinumab led to 95% of patients reaching PASI75 by Week 12 of treatment.[3] This quality suggests utility for patients under circumstances where injections have been missed.

Secukinumab has the highest adherence rate out of all the IL-17 inhibitors, ranging from 46–52% at 9 months of treatment.[21] This may be because it is one of the best-tolerated biologics in terms of injection site reactions.[3] Compared to all the other IL-17 inhibitors, secukinumab had the most extensive safety record in terms of patient data, and no black box warnings currently exist.[3] Only a very mild increase in superficial fungal and yeast infections has been observed.[3] The incidence of new-onset inflammatory bowel disease (IBD) is less than 1 out of 1,000 patients on secukinumab, but increased side effects have been documented among patients with IBD taking secukinumab for other conditions.[3,22] Therefore, it should be used with caution in these patients.[5]

Ixekizumab

Ixekizumab is a humanised IgG4 monoclonal antibody with high affinity against IL-17A.[3] The regimen requires an initial loading dose of 160 mg SQ at Week 0, followed by 80 mg SQ at Weeks 2, 4, 6, 8, 10, and 12.[3] Maintenance dosing is 80 mg SQ every 4 weeks.[3]

In terms of efficacy, in the UNCOVER-1, -2, and -3 RCTs, ixekizumab showed a PASI75 of 83% and PASI90 of 67%.[19] It is also the fastest-acting biologic.[3] Ixekizumab is FDA-approved for plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.[3] It is also the only biologic with FDA approval for the treatment of genital psoriasis.[3] In a real-life case series of adult patients affected by genital psoriasis, ixekizumab significantly improved disease severity, itch, and QoL.[23]

A relatively higher rate of injection site reactions and pain has been reported with ixekizumab; however, during Phase III trials, 97% of patients did not consider this significant enough to stop treatment, and the reactions improved over the treatment course.[3,24] Ixekizumab is now formulated without citrate to reduce injection site complaints.[25] Concern regarding the risk of IBD exists and warrants caution when using ixekizumab in these patients. However, the incidence of new-onset IBD in patients on ixekizumab is less than one out of 1,000.[3] Additionally, data from an integrated database of seven ixekizumab trials found the prevalence of IBD cases to be less than 1%.[5] Lastly, there is a slight increase in superficial yeast and fungal infections in patients on ixekizumab.[3]

Ixekizumab has shown the highest cumulative clinical benefits for complete skin clearance and the highest cumulative days at PASI100 (23 weeks of the year) relative to guselkumab, secukinumab, and TNF-α inhibitors.[6] Ixekizumab also has the best patient satisfaction, attitude, and self-reported improvement scores compared to secukinumab and ustekinumab.[12] In a real-life retrospective observational study, ixekizumab led to a rapid and progressive improvement in average PASI and patient satisfaction, and the clinical results were maintained for up to 4 years of continuous treatment.[26] These results were not influenced by specific factors such as gender, previous biologic therapies, and average BMI.[26]

In another study population of patients with difficult-to-treat psoriasis and a poor response to TNF-α inhibitors, ixekizumab was significantly better than placebo in improving symptoms of disease, and this further correlated with improved mental symptoms, such as better mood and self-esteem.[22] In another study of patients with psoriasis with moderately severe depressive symptoms, a 12-week course of ixekizumab

showed improved remission rates of depression for 40% of patients, along with decreased parameters of systemic inflammation.[22] Ixekizumab has the second-highest adherence rates out of the IL-17 inhibitors, following secukinumab, at 46% after 9 months of treatment.[21]

Brodalumab

Brodalumab is a humanised monoclonal antibody that binds the IL-17A receptor subunit, and blocks the activities of not only IL-17A but also IL-17F, IL-17A/F, and IL-17E.[3] The initial loading dose for brodalumab is 210 mg SQ at Weeks 0, 1, and 2, followed by a maintenance dose of 210 mg SQ every 2 weeks.[3]

In terms of efficacy, in the AMAGINE-2 and -3 RCTs, brodalumab showed a PASI75 of 85% and PASI90 rate of 70%.[19] Brodalumab has a strong efficacy and rapid onset of action.[3] In a single-centre, real-life, retrospective study, brodalumab showed a significant reduction in mean PASI and body surface area, and was comparable to ixekizumab in terms of efficacy and safety.[27]

Brodalumab has a black box warning for suicide and suicidal ideation. While clinical trials did note the presence of suicidal ideation and behaviours in patients, subsequent detailed analysis of these trials failed to identify a causal association between the drug and these events.[5] Furthermore, it was found that patients were not excluded for history of suicidal ideation/behaviour or illicit drug/alcohol history, suggesting a potential confounding effect.[3] Currently, the USA is the only country with this black box warning.[3,28] There have also been higher rates of superficial skin infections seen with brodalumab, which may be attributed to the more extensive blockade on multiple aspects of the IL-17 receptor.[24] Lastly, caution should still be taken when considering brodalumab for patients with existing IBD. In a study on patients with moderate-to-severe Crohn's disease, brodalumab was ineffective and caused increased exacerbations in those patients with active disease.[22] This finding was also observed in a Phase II RCT evaluating the efficacy of brodalumab in treatment of Crohn's disease.[5]

An advantage of brodalumab is its significantly lower cost of treatment combined with high PASI rates, rendering it the most cost-effective choice for treatment of moderate-to-severe psoriasis.[3] In comparison to other biologics, brodalumab was shown to have the third-highest cumulative clinical benefit for skin clearance, along with the third-highest cumulative days at PASI100.[6] Lastly, brodalumab was found to have the highest efficacy in complete skin clearance as early as Weeks 4 and 8 of treatment.[11]

Bimekizumab

Bimekizumab is a humanised IgG1κ monoclonal antibody that selectively inhibits the IL-17A and IL-17F cytokines.[29] While it is still pending FDA approval, bimekizumab has shown a high degree of skin clearance with rapid onset of action and persistent results over time.[29,30] Phase III trials have demonstrated superior efficacy and clinical results compared to placebo, adalimumab, ustekinumab, and secukinumab.[31] In a recent network meta-analysis, bimekizumab was statistically superior to all other biologics in attaining PASI90 and PASI100 levels.[32] The most commonly reported safety concern is oral candidiasis, but most cases have been mild-to-moderate and do not necessitate cessation of treatment.[31] The IL-17 pathway is involved in inhibiting fungal infections, and while this is an adverse effect known in all IL-17 inhibitors, it is more common with bimekizumab.[31]

In the BE READY Phase III RCT, bimekizumab's clinical efficacy was sustained for 8 months after discontinuation, indicating its high clinical durability.[31] Additionally, given adherence to medical treatment may be improved with a regimen of less-frequent dosing, bimekizumab's maintenance regimen offers an advantage, as the schedule may be every 4 weeks or every 8 weeks, versus the every-4-week regimen of secukinumab and ixekizumab and the every-2-week regimen of brodalumab.[31]

IL-23 Inhibitors

Guselkumab

Guselkumab is a completely human IgG1γ monoclonal antibody that blocks the p19 subunit of IL-23.[33,34] The dosing regimen for this biologic agent is an initial loading dose of 100 mg SQ at Weeks 0 and 4, followed by 100 mg SQ as maintenance dosing every 8 weeks.[3] Guselkumab is FDA-approved for psoriatic arthritis.

In terms of efficacy, in the VOYAGE-1 RCT, guselkumab showed a PASI75 of 91% and PASI90 of 73%.[19] The ECLIPSE study found guselkumab to have superior long-term efficacy based on PASI90 at Week 48 compared to secukinumab.[34] In real-life studies, guselkumab has shown considerable efficacy and safety in real-world clinical practice for up to 3 years of treatment.[35-37] It is also a valuable option for patients with psoriasis who have previously failed anti-IL17 treatments.[35] Guselkumab has also shown the highest overall drug survival associated with effectiveness and safety compared to other biologics.[38]

Results from VOYAGE 2 found guselkumab to be associated with greater improvements in symptoms of anxiety and depression in patients with psoriasis when compared to a placebo and adalimumab.[5]

Guselkumab has no FDA warnings for an increased risk of infections from superficial tinea or candidiasis.[3] There also have been no reports of an increased risk of IBD.[3] In a comparison to adherence rates among adalimumab, certolizumab, etanercept, guselkumab, ixekizumab, secukinumab, and ustekinumab, guselkumab had an adherence rate of 56.9% at 9-month follow-up, which was second-highest after ustekinumab.[21]

Risankizumab

Risankizumab is a fully humanised IgG1 monoclonal antibody that selectively targets the p19 subunit of IL-23.[39] The dosing regimen begins with 150 mg SQ injections given at Weeks 0 and 4 for initiation.[3] The maintenance dose is 150 mg every 12 weeks for a total of 4 injections annually.[3] Risankizumab is FDA-approved for psoriasis and psoriatic arthritis.

In terms of efficacy, risankizumab achieved a PASI90 rate of 75.3% in the UltIMMa-1 Phase III trial.[40] The UltIMMa-1 and -2 clinical trials showed that risankizumab has superior efficacy to both placebo and ustekinumab.[40,41] This agent has a quick onset of action and high durability of 295 days for recurrence after discontinuing treatment.[3,42,43]

Risankizumab has the second-highest cumulative clinical benefits in regards to total skin clearance.[6] Compared to other psoriasis treatments, risankizumab has the most favourable long-term benefit-risk profile due to its excellent PASI response rate and lowest rate of adverse events (AE).[44] Available data demonstrates that risankizumab is safe and well-tolerated at 58 months.[3] Serious AEs in the NCT02054481 trial[45] included two patients with basal cell carcinoma, one patient with a myocardial infarction, and one patient with a cerebrovascular accident;[40] however, there was no significant difference in rates of AEs across all the groups in the Gordon et al. trial.[41] In real-life studies, risankizumab has shown high efficacy in treatment of difficult-to-treat areas (scalp, nails, genitalia, lower limbs, and palmo-plantar area) and in patients with psoriasis who have previously failed anti-IL17 treatments.[46,47]

Tildrakizumab

Tildrakizumab is a humanised IgG1 monoclonal antibody designed to target the p19 subunit of IL-23.[2,3] The initial loading dose is 100 mg SQ at Weeks 0 and 4, followed by a maintenance dose of 100 mg every 12 weeks.[3] Tildrakizumab is readily covered by Medicare Part B.[3] Thus, it cannot be self-administered; patients must receive their injections at injection or infusion centres, including their provider's office. Since there are only four maintenance injections per year, given its long half-life, this is a favourable regimen for long-term management and adherence.[3,48]

In terms of efficacy, in the reSURFACE-1 and -2 RCTs, tildrakizumab had a PASI75 of 61–64% and PASI90 of 35–39%.[19] Real-life studies have shown similar reported efficacy and safety, without significant risk of AEs even in more fragile patients (such as the elderly population) and in other forms of psoriasis such as erythrodermic psoriasis.[49,50] In a real-world observational study, tildrakizumab also provided considerable efficacy in treatment of difficult-to-treat areas.[46]

Tildrakizumab had the least number of AEs occurring in at least 1% in Phase II trials of all biologics for psoriasis, which may be an important consideration for clinicians interested in safety, especially in elderly patients.[3] The long-term incidence of AEs of special interest was comparable with results from the psoriasis reference population captured in the Psoriasis Longitudinal Assessment and Registry.[51]

There was no specific association with or worsening of IBD and only one suspected case of new-onset Crohn's disease over the course of 5 years of treatment.[48,51] Thaci et al.[51] reported no severe cases of candidiasis in a pooled analysis of two randomised Phase III clinical trials over a 5-year period. Studies have reported improved Dermatology Life Quality Index (DLQI) metrics with tildrakizumab that correlated with Week 28 PASI improvement.[48,49] Patients that failed to achieve a minimum of 50% PASI improvement at Week 28 could be differentiated as early as Week 8 from their PASI score.[48,49] This suggests that an informed decision about whether or not to continue tildrakizumab therapy can be made before the third dose, around Week 12 or 16.[52]

IL-12/23 Inhibitor

Ustekinumab

Ustekinumab is a biologic agent that inhibits the p40 subunit of both IL-12 and the IL-23.[53] The dosing for this biologic is weight-dependent.[3] For patients who weigh less than 100 kg, there is an initial loading dose of 45 mg SQ at Weeks 0 and 4, followed by 45 mg maintenance injections every 12 weeks.[3] For patients who weigh more than 100 kg, the initial loading dose is 90 mg SQ at Weeks 0 and 4, followed by maintenance doses of 90 mg every 12 weeks.[3]

Ustekinumab has shown high efficacy and a favourable safety profile.[54] In patients who had a response to this biologic at Week 40 and continued maintenance treatment, 80.9% of the patients who were taking 45 mg and 82.7% taking 90 mg achieved a PASI75 response at Year 3 of treatment.[55] Ustekinumab is FDA-approved for treatment of psoriatic arthritis and IBD.[3] Although it has lower efficacy values than newer biologics, ustekinumab is the biologic that is least frequently discontinued due to loss of efficacy.[3,54,56]

Ustekinumab is one of the most expensive biologics, but its sporadic dosing regimen gives it a favourable cost-efficacy profile.[54] Many patients favour the every 12 weeks maintenance schedule.[53] For up to 3 years of follow-up, ustekinumab was generally well tolerated, and none of the reported AEs necessitated treatment discontinuation.[55] Ustekinumab has a satisfaction rating of 77%, which is the highest rating for biologics.[54,55] Patients using ustekinumab have reported significantly higher perceived improvement of disease compared to those using other biologics.[12]

DISCUSSION

Overall, patients tend to view systemic psoriasis treatments positively and report high treatment satisfaction scores.[12] Patients with psoriasis using biologics specifically have shown higher rates of satisfaction with improved skin clearance, long-term efficacy, rapidity of response, and significantly lower risk of AEs as compared to those using non-biologics.[57] While users may initially express hesitation or concern due to the mode of administration, these feelings tend to dissipate with appropriate counselling, education, and familiarity over time.[57] Good communication between the clinician and patient is a significant positive predictor of treatment satisfaction and success.[12]

The most common reasons for treatment discontinuation and/or switching to a new medication are loss of efficacy with time and AEs, followed by overall ineffectiveness and high expense of treatment.[54,58,59] Commonly reported obstacles to obtaining biologic treatment are issues with insurance approval, cost of treatment, and difficulties related to the pharmacy.[58]

While cessation of treatment is not recommended and will likely lead to a relapse, it may be necessary under certain circumstances such as financial strain, intolerable side effects, pregnancy, scheduled surgery, and extended travel with reduced access to healthcare.[60] If such situations are known in advance, it is important to consider the benefits of biologic use in these conditions.

Biologics have shown a longer duration of sustained response after cessation of use compared to oral systemics.[60] The IL-12/23 and IL-23 inhibitors have shown the longest time to relapse (defined by the loss of PASI90), with a duration of 21–42 weeks.[60] The IL-17 inhibitors have an average time to relapse of 7–24 weeks, and the TNF-α inhibitors have an average time to relapse of 4 weeks.[60]

For both the clinician and patient, long-term benefits and risks associated with treatment are important to discuss when choosing a biologic.[44] All biologic drugs have shared side effects depending largely on the class of biologic.[61] The most common side effects associated with the IL-17 inhibitors include headache, nasopharyngitis, and infections.[31] This class of biologics is also most notably associated with induction or worsening of IBD.[31,62] The most common side effects associated with the IL-23 inhibitors include nasopharyngitis, upper respiratory tract infections, and injection site reactions.[3,33,55] Collectively, IL-17 and IL-23 inhibitors have good safety profiles and are largely well-tolerated by patients.[61]

CONCLUSION

The newer biologics available for treatment of moderate-to-severe plaque psoriasis in adults have shown undisputable superiority in many parameters to older treatment options. Given the significance of this therapeutic arsenal, it is important for providers to be both familiar and comfortable with determining the optimal biologic of choice for each patient. These factors include patient preference and goals, safety, cost, long-term efficacy, rapidity of response, comorbidities, biologic naivety, and the unique features of each biologic described in this review.

The landscape of psoriasis treatment will certainly continue to evolve as researchers identify new potential therapeutic targets, creating a promising future for the treatment of this frequently debilitating and recalcitrant disease.

References

1. Raharja A et al. Psoriasis: a brief overview. Clin Med. 2021;21(3):170-3.
2. Girolomoni G et al. The role of IL-23 and the IL-23/T_H 17 immune axis in the pathogenesis and treatment of psoriasis. J Eur Acad Dermatol Venereol. 2017;31(10):1616-26.
3. Brownstone N et al. Biologic treatments of psoriasis: an update for the clinician. Biologics. 2021;15:39-51.
4. Azhar A et al. Ixekizumab in the treatment of moderate-to-severe plaque psoriasis: patient adherence, satisfaction, and preferences. Dermatol Ther. 2021;34(1):e14486.
5. Monks G et al. The psoriasis decision tree. J Clin Aesthetic Dermatol. 2021;14(4):14-22.
6. Blauvelt A et al. Cumulative clinical benefits of biologics in the treatment of patients with moderate-to-severe psoriasis over 1 year: a network meta-analysis. Dermatol Ther. 2022;12(3):727-40.
7. Kaushik SB, Lebwohl MG. Psoriasis: which therapy for which patient: psoriasis comorbidities and preferred systemic agents. J Am Acad Dermatol. 2019;80(1): 27-40.
8. Alcusky M et al. Dermatologist and patient preferences in choosing treatments for moderate to severe psoriasis. Dermatol Ther. 2017;7(4):463-83.
9. van Cranenburgh OD et al. Satisfaction with treatment among patients with psoriasis: a web-based survey study. Br J Dermatol. 2013;169(2):398-405.
10. Chaudri NA. Adherence to long-term therapies evidence for action. Ann Saudi Med. 2004;24(3):221-2.
11. Leonardi CL et al. Number needed to treat network meta-analysis to compare biologic drugs for moderate-to-severe psoriasis. Adv Ther. 2022;39(5):2256-69.
12. Esposito M et al. Satisfaction and attitudes toward systemic treatments for psoriasis: cross-sectional study. Dermatol Ther. 2021;34(3):e14949.
13. Janssen Inc., Clinical Review Report: Guselkumab (Tremfya) [Internet] (2018) Ottawa: Canadian Agency for Drugs and Technologies in Health. Available at: http://www.ncbi.nlm.nih.gov/books/NBK534047/. Last accessed: 18 July 2022.
14. Carlin CS et al. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004;50(6):859-66.
15. Gerdes S et al. Real-world effectiveness of guselkumab in patients with psoriasis: health-related quality of life and efficacy data from the noninterventional, prospective, German multicenter PERSIST trial. J Dermatol. 2021;48(12):1854-62.
16. Ruggiero A et al. Real world practice indirect comparison between guselkumab and risankizumab: results from an Italian retrospective study. Dermatol Ther. 2022;35(1):e15214.
17. Ruggiero A et al. Ocular Manifestations in Psoriasis Screening (OcMaPS) Questionnaire: a useful tool to reveal misdiagnosed ocular involvement in psoriasis. J Clin Med. 2021;10(5):1031.
18. Megna M et al. Efficacy and safety of biologics and small molecules for psoriasis in pediatric and geriatric populations. Part II: focus on elderly patients. Expert Opin Drug Saf. 2023;22(1):1-16.
19. Stein Gold LF et al. Understanding topical therapies for psoriasis. Cutis. 2019;103(4S):S8-12.
20. Avallone G et al. Real-life comparison between secukinumab and ixekizumab in the treatment of pustular and erythrodermic psoriasis. J Eur Acad Dermatol Venereol. 2022;36(7):e574-6.
21. Xu C et al. Drug adherence and persistence of patients with moderate to severe psoriasis treated with biologic medications

in a US commercially insured population. Dermatology. 2022;238(3):438-47.

22. Berry SPDG et al. The role of IL-17 and anti-IL-17 agents in the immunopathogenesis and management of autoimmune and inflammatory diseases. Int Immunopharmacol. 2022;102:108402.
23. Calianno G et al. Ixekizumab improves disease severity, clinical symptoms and quality of life in patients with genital psoriasis: a 24-week real-life experience. Dermatol Ther. 2021;34(4):e14993.
24. Palakornkitti P et al. Biological therapy in psoriasis: an emphasis on its dermatologic adverse events. Asian Pac J Allergy Immunol. 2021;39(4):215-30.
25. Chabra S et al. Ixekizumab citrate-free formulation: results from two clinical trials. Adv Ther. 2022;39(6):2862-72.
26. Malagoli P et al. Real life long-term efficacy and safety of ixekizumab in moderate-to-severe psoriasis: a 192 weeks multicentric retrospective study—IL PSO (Italian landscape psoriasis). Dermatol Ther. 2022;35(8):e15608.
27. Megna M et al. Ixekizumab and brodalumab indirect comparison in the treatment of moderate to severe psoriasis: results from an Italian single-center retrospective study in a real-life setting. Dermatol Ther. 2022;35(9):e15667.
28. Reich K et al. Long-term efficacy and safety of brodalumab in moderate-to-severe plaque psoriasis: a post hoc pooled analysis of AMAGINE-2 and -3. J Eur Acad Dermatol Venereol. 2022;36(8):1275-83.
29. Zozaya N et al. Assessing the value contribution of bimekizumab for the treatment of moderate-to-severe psoriasis using a multidisciplinary reflective multi-criteria decision analysis. Expert Rev Pharmacoecon Outcomes Res. 2022;22(6):941-53.
30. Ruggiero A et al. Bimekizumab for the treatment of psoriasis: a review of the current knowledge. Psoriasis Targets Ther. 2022;12:127-37.
31. Freitas E et al. Bimekizumab for the treatment of psoriasis. Drugs. 2021;81(15):1751-62.
32. Armstrong A et al. Efficacy of bimekizumab and other biologics in moderate to severe plaque psoriasis: a systematic literature review and a network meta-analysis. Dermatol Ther. 2022;12(8):1777-92.
33. Blauvelt A et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405-17.
34. Reich K et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. Lancet Lond Engl. 2019;394(10201):831-9.
35. Megna M et al. Guselkumab is efficacious and safe in psoriasis patients who failed anti-IL17: a 52-week real-life study. J Dermatol Treat. 2022;33(5):2560-64.
36. Megna M et al. Long-term efficacy and safety of guselkumab for moderate to severe psoriasis: a 3-year real-life retrospective study. Psoriasis Auckl NZ. 2022;12:205-12.
37. Snast I et al. Real-life experience of guselkumab in patients with psoriasis. Dermatol Ther. 2020;33(6):e13964.
38. Yiu ZZN et al. Drug survival associated with effectiveness and safety of treatment with guselkumab, ixekizumab, secukinumab, ustekinumab, and adalimumab in patients with psoriasis. JAMA Dermatol. 2022;158(10):1131-41.
39. Haugh I et al. Risankizumab: an anti-IL-23 antibody for the treatment of psoriasis. Drug Des Devel Ther. 2018;12:3879-83.
40. Gu C, Yang J. Risankizumab for the treatment of psoriasis. Expert Rev Clin Pharmacol. 2019;12(9):851-7.
41. Gordon KB et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018;392(10148):650-61.
42. Kristensen LE et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. Ann Rheum Dis. 2022;81(2):225-31.
43. Östör A et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. Ann Rheum Dis. 2022;81(3):351-8.
44. Armstrong AW et al. Long-term benefit–risk profiles of treatments for moderate-to-severe plaque psoriasis: a network meta-analysis. Dermatol Ther. 2022;12(1):167-84.
45. Boehringer Ingelheim. BI 655066 dose ranging in psoriasis, active comparator ustekinumab. NCT02054481. https://clinicaltrials.gov/ct2/show/results/NCT02054481.
46. Megna M et al. Real-world practice indirect comparison between guselkumab, risankizumab, and tildrakizumab: results from an Italian 28-week retrospective study. J Dermatol Treat. 2022;33(6):2813-20.
47. Megna M et al. Risankizumab treatment in psoriasis patients who failed anti-IL17: a 52-week real-life study. Dermatol Ther. 2022;35(7):e15524.
48. Sinclair R et al. Tildrakizumab for the treatment of psoriasis. Expert Rev Clin Immunol. 2019;15(1):5-12.
49. Ruggiero A et al. Tildrakizumab for the treatment of moderate to severe psoriasis: results from a single center preliminary real-life study. Dermatol Ther. 2022;35(12):e15941.
50. Ruggiero A et al. Drug safety evaluation of tildrakizumab for psoriasis: a review of the current knowledge. Expert Opin Drug Saf. 2022;21(12):1445-51.
51. Thaci D et al. Five-year efficacy and safety of tildrakizumab in patients with moderate-to-severe psoriasis who respond at week 28: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2)*. Br J Dermatol. 2021;185(2):323-34.
52. Blauvelt A et al. Tildrakizumab efficacy and impact on quality of life up to 52 weeks in patients with moderate-to-severe psoriasis: a pooled analysis of two randomized controlled trials. J Eur Acad Dermatol Venereol. 2019;33(12):2305-12.
53. Alunno A et al. Targeting the IL-23/IL-17 axis for the treatment of psoriasis and psoriatic arthritis. Expert Opin Biol Ther. 2015;15(12):1727-37.
54. Piragine E et al. Adherence and persistence to biological drugs for psoriasis: systematic review with meta-analysis. J Clin Med. 2022;11(6):1506.

55. Kimball AB et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial through up to 3 years: long-term efficacy of ustekinumab in moderate-to-severe psoriasis. Br J Dermatol. 2012;166(4):861-72.
56. Pilon D et al. Risk of treatment discontinuation among patients with psoriasis initiated on ustekinumab and other biologics in the USA. Dermatol Ther. 2022;12(4):971-87.
57. Ighani A et al. Satisfaction and awareness of systemic psoriasis treatments: a national survey comparing biologic and nonbiologic users. J Cutan Med Surg. 2019;23(2):148-56.
58. Kamangar F et al. How psoriasis patients perceive, obtain, and use biologic agents: survey from an academic medical center. J Dermatol Treat. 2013;24(1):13-24.
59. Kamangar F et al. How psoriasis patients perceive, obtain, and use biologic agents: Survey from an academic medical center. J Dermatolog Treat. 2013;24(1): 13-24.
60. Masson Regnault M et al. Time to relapse after discontinuing systemic treatment for psoriasis: a systematic review. Am J Clin Dermatol. 2022;23(4):433-47.
61. Loft ND et al. Adverse events with IL-17 and IL-23 inhibitors for psoriasis and psoriatic arthritis: a systematic review and meta-analysis of phase III studies. J Eur Acad Dermatol Venereol. 2020;34(6):1151-60.
62. Kojanova M et al. Efficacy, safety, and drug survival of patients with psoriasis treated with IL-17 inhibitors – brodalumab, ixekizumab, and secukinumab: real-world data from the Czech Republic BIOREP registry. J Dermatol Treat. 2022:33(6):2827-37.

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