Clinical relevance of type 2 inflammation as a driver of multi-organ disease: A Delphi consensus initiative

Unnur Steina Björnsdóttir[1], Mette Deleuran[2], Christer Janson[3], Mika Makela[4], Celeste Porsbjerg[5], Sanna Toppila-Salmi[4], Kasper Aanæs[6], Tove Agner[7], Lars Ahlbeck[8], Alan Altraja[9], Leif Bjermer[10], Maria Bradley[11], Lars Olaf Cardell[12], Sven-Erik Dahlén[13], Kilian Eyerich[11], Gunilla Hedlin[14], Theis Huldt-Nystrøm[15], Stein Øyvind Jørstad[16], Hannu Kankaanranta[17], Jussi Karjalainen[18], Laura Korhonen[19], Lauri Lehtimäki[18], Johanna Mandelin[4], Anita Remitz[4], Andreas Sonesson[20], Sverre Steinsvåg[21], Simon Francis Thomsen[7], Charlotte Ulrik[22], Christian Vestergaard[2], and Jacob Thyssen[7]

[1]Department of Pulmonary Medicine and Allergy/Clinical Immunology University of Iceland Reykjavík Iceland
[2]Department of Dermatology and Venereology Åarhus University Hospital Åarhus Denmark
[3]Department of Medical Sciences Uppsala University Uppsala Sweden
[4]Skin and Allergy Hospital University of Helsinki and Helsinki University Hospital Helsinki Finland
[5]Department of Respiratory Medicine Bispebjerg Hospital Copenhagen Denmark
[6]Department of Otorhinolaryngology Head and Neck Surgery and Audiology University of Copenhagen Copenhagen Denmark
[7]Department of Dermatology Bispebjerg University Hospital Copenhagen Denmark
[8]Allergy Center University Hospital Linköping Sweden
[9]Department of Pulmonology University of Tartu and Lung Clinic Tartu University Hospital Tartu Estonia
[10]Department of Respiratory Medicine and Allergology Skåne University Hospital Lund Sweden
[11]Dermatology and Venereology Unit Department of Medicine Karolinska University Hospital Stockholm Sweden
[12]Department of Clinical Sciences Intervention and Technology Karolinska Institutet Stockholm Sweden
[13]Experimental Asthma and Allergy Research Karolinska Institutet Stockholm Sweden
[14]Department of Women's and Children's Health and Centre for Allergy Research Karolinska Institutet Stockholm Sweden
[15]Hudpoliklinikken Namsos Norway
[16]Southern and Eastern Norway Regional Health Authority Fredrikstad Norway
[17]Department of Respiratory Medicine Seinäjoki Central Hospital Seinäjoki Finland
[18]Allergy Centre Tampere University Hospital Tampere Finland
[19]Department of Dermatology Tampere University Hospital Tampere Finland Faculty of Medicine and Health Technology University of Tampere Tampere Finland
[20]Department of Dermatology and Venereology Clinical Sciences Skåne University Hospital Lund University Lund Sweden

[21]Department of Otolaryngology Sørlandet Hospital Kristiansand Norway
[22]Department of Respiratory Medicine Copenhagen University Hospital-Hvidovre Hvidovre Denmark

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Abstract

Background: This initiative aimed to elucidate the clinical relevance of type 2 (T2) inflammation as a driver of asthma, atopic dermatitis, chronic rhinitis, chronic rhinosinusitis with nasal polyps (CRSwNP) and eosinophilic esophagitis. **Methods:** A steering committee (SC) conducted a non-systematic literature search to inform the design of a Delphi questionnaire including 23 consensus statements, which was circulated to 30 experts including the SC. Experts rated their agreement with each statement on a 9-point Likert scale and provided optional feedback that was used to develop a second Delphi questionnaire. On 22 October 2020, a meeting was held to discuss the conclusions from the questionnaires and explore how this initiative may impact the management of patients with T2 inflammation-driven disease. Post meeting, a consensus statement on the role of T2 inflammation in eosinophilic esophagitis was circulated to the experts. **Results:** It was agreed that T2 inflammation may be an underlying driver of asthma, atopic dermatitis, chronic rhinitis, CRSwNP and eosinophilic esophagitis, and that the published evidence suggests that these diseases overlap. Some of this overlap may include related multimorbid conditions driven by T2 inflammation. Thus, in patients with multiple T2 inflammation-driven diseases, a cross-speciality approach is warranted to provide effective care. A question guide with input from relevant experts was proposed, to identify comorbidities and facilitate appropriate holistic patient management. **Conclusions:** These consensus recommendations should be used as a framework to further understand the extent of T2 inflammation-driven multi-organ disease and to improve the holistic management and care of these patients.

INTRODUCTION

A type 2 immune response is triggered by the activation of T helper 2 (Th2) cells and/or innate lymphoid type 2 cells (ILC2), leading to the expression of type 2 inflammatory cytokines such as interleukin (IL)-4, IL-5 and IL-13,[1,2] as well as IL-31 in the skin (Figure 1A).[3] Type 2 inflammation can be characterised by the elevation of biomarkers such as immunoglobulin E (IgE), blood and/or tissue eosinophils, and elevated fractional exhaled nitric oxide (FeNO).[1,2,4]

Type 2 inflammation has been identified as a key driver of the pathogenesis of various diseases such as allergic asthma,[5,6] non-allergic eosinophilic asthma,[7] atopic dermatitis,[6,8]chronic rhinitis,[6,9] chronic rhinosinusitis with nasal polyps (CRSwNP)[6,10] and eosinophilic esophagitis,[11-13] and as an important pathogenic cofactor in chronic urticaria, food allergy and conjunctivitis (Figure 1B–E).[14,15] Although co-occurrence of these diseases in individual patients has been reported, the heterogeneity of epidemiological studies makes it difficult to draw valid conclusions about the extent of multi-organ disease driven by type 2 inflammation.[16-28]

Inhibition of IL-13[29-32] and IL-4 receptor (R)[33-35] is effective for the treatment of asthma, atopic dermatitis and CRSwNP. Inhibition of IL-4R,[34]IL-5[36] and IL-5R[37] is effective for the treatment of patients with asthma, but IL-5 inhibition lacked efficacy in a short study of mepolizumab in patients with atopic dermatitis.[38] Inhibition of IL-13[39], IL-4R[40], IL-5[41] and IgE[42] is effective for the treatment of eosinophilic esophagitis.

IL-31 is a potent pruritogenic cytokine that is involved in type 2 inflammation and may be a potential novel target for the treatment of pruritus in patients with atopic dermatitis.[43] In addition, thymic stromal lymphopoietin, an epithelial-cell-derived cytokine that has a major role in type 2 inflammation, is being investigated as a target for the treatment of type 2 inflammation-driven diseases.[44]

In patients with asthma, biomarkers such as FeNO and blood eosinophils are predictive biomarkers of response to corticosteroids and biologic agents targeting type 2 inflammation.[45] The discovery of this associa-

tion has led to a paradigm shift in the treatment of severe asthma. Many biomarkers have been identified that assist with characterising the subtypes of CRSwNP, such as eosinophil count and bitter/sweet taste receptors, but biomarkers linked to the intrinsic biomolecular mechanism of the disease are needed.[46]Biomarkers of treatment response for eosinophilic esophagitis, such as microRNAs, are currently being investigated.[47] The future discovery of biomarkers in type 2 inflammation-driven diseases has the potential to enable accurate phenotyping, tailored management and a deeper understanding of the variation of immunological drivers behind the diseases.

There is a need to discuss the extent to which type 2 inflammation is the underlying cause of multi-organ disease, as this may have important implications for patient management and prognosis. To address this need, Sanofi Genzyme invited a group of experts representing different relevant specialties (allergy; clinical immunology; dermatology; ear, nose, and throat [ENT]; internal medicine; paediatrics; respiratory) from the Nordic region (Denmark, Estonia, Finland, Iceland, Norway, Sweden), based on their expertise related to the treatment of patients with type 2 inflammatory diseases in their respective fields, to gather for a consensus meeting using a modified Delphi process. The consensus meeting aimed to identify, in the clinical points of view of the experts, which diseases are predominantly driven by type 2 inflammation, assess the extent of multi-organ disease, evaluate whether the diseases can be considered to belong to the same spectrum of type 2 inflammation-driven multi-morbidities rather than being distinct primary diseases and comorbidities, and outline the impact on the holistic management of patients presenting with diseases related to type 2 inflammation.

Methods

Steering committee and expert meeting attendees

A steering committee (SC) was formed that comprised seven experts from across the Nordic region who were invited by Sanofi Genzyme based on their expertise in their respective fields related to the treatment of patients with type 2 inflammatory diseases. The SC members included one allergist and clinical immunologist from Iceland, two dermatologists from Denmark, one ENT specialist from Finland, one paediatrician from Finland and two pulmonologists from Sweden and Denmark, respectively. In addition to the SC, 23 experts (dermatologists [n = 10], pulmonologists [n = 7], ENT specialists [n = 3], internal medicine specialists/clinical immunologists/allergists [n = 2] and a paediatrician) from across the Nordic region (Sweden [n = 8], Finland [n = 6], Denmark [n = 5], Norway [n = 3] and Estonia [n = 1]) were invited to participate. All were considered widely recognised experts in their fields at least at a regional level.

Scope

The SC determined the scope of this initiative, which investigated the extent of overlap between diseases that may be driven by type 2 inflammation (asthma, atopic dermatitis, CRSwNP, eosinophilic esophagitis and chronic rhinitis). There are other relevant conditions, such as food allergy and chronic urticaria, that were not included.

Literature search

To improve the knowledge base for the discussion, a non-systematic literature search was performed using the PubMed database to identify published work related to the objectives of this study and to identify needs for consensus. The literature search was conducted between January and June 2020 and included multiple combinations of the following search terms: ‘atopic dermatitis’, ‘atopic eczema’, ‘childhood eczema’, ‘paediatric eczema’, ‘asthma’, ‘rhinitis’, ‘eosinophilic esophagitis’, ‘chronic rhinosinusitis’ and ‘polyps’, with ‘morbidities’ added as a qualifier. Searches for ‘atopic march’ and ‘allergic rhinitis and its impact on asthma

(ARIA)' were also conducted. Publications were only considered if they were written in English, had a human/clinical focus and were published after 1 January 2005.

The most relevant papers were identified based on review of abstracts; relevant data regarding the prevalence of overlap between type 2 inflammatory conditions were extracted and tabulated according to primary diagnosis. Reference lists of key papers and papers of interest provided by the SC were also reviewed.

Modified Delphi process

The Delphi process is a recognised facilitation technique used to obtain consensus between specialists in a particular field where expert opinion is important for clinical guidance, especially if limited evidence is available.[48] This approach provides experts with the opportunity to alter their response based on their peers' opinions, thus increasing the likelihood for opinions to converge. The modified Delphi process used in this initiative is outlined in Figure 2.

Results

Type 2 inflammation and related diseases

The experts agreed that a simple definition of the underlying immunopathology of type 2 inflammation is Th2 cell and/or ILC2 activation with expression of type 2 inflammatory cytokines such as IL-4, IL-5 and IL-13 (Table 1). In addition, type 2 inflammation can be characterised by the elevation of biomarkers such as IgE, blood and/or tissue eosinophils, and, in asthma, elevated FeNO. Type 2 inflammation may be considered as an underlying immunopathological driver of some endotypes of asthma, atopic dermatitis, chronic rhinitis, CRSwNP and eosinophilic esophagitis.

The published epidemiological evidence suggests that there is some overlap in the occurrence of asthma, atopic dermatitis, chronic rhinitis, CRSwNP and eosinophilic esophagitis in adults (Table 2) and in the occurrence of asthma, atopic dermatitis, chronic rhinitis and eosinophilic esophagitis in children (Table 3). However, in both populations, the available evidence is too heterogenous to permit valid conclusions to be drawn about the extent of the overlap.

It was acknowledged that asthma and atopic dermatitis can coexist in adults and children, that asthma and chronic rhinitis coexist in some adults and children and that asthma and CRSwNP coexist in some adult patients. In addition, patients with adult-onset asthma and CRSwNP have a distinct subset of asthma that often presents clinically with a disease that is more difficult to manage compared with other subsets of asthma. However, consensus was not achieved regarding the pattern of overlap between asthma, atopic dermatitis, chronic rhinitis and CRSwNP with or without eosinophilic esophagitis. During the virtual meeting, consensus might have been reached if the consensus statement had been revised to 'pattern of selected overlap', to clarify that patients rarely have all these diseases simultaneously.

In the experts' clinical experience, the presence of more than one atopic disease such as asthma, atopic dermatitis, chronic rhinitis, CRSwNP or eosinophilic esophagitis often predisposes patients to more severe disease compared with patients suffering from only one of these diseases. In addition, in the experts' clinical experience, type 2 inflammation may drive mild, moderate and severe forms of asthma, atopic dermatitis, chronic rhinitis, CRSwNP and eosinophilic esophagitis. Some overlap between asthma, atopic dermatitis, chronic rhinitis, CRSwNP and eosinophilic esophagitis may be considered as a set of related multimorbid conditions driven by underlying type 2 inflammation.

Management of patients with type 2 inflammatory diseases

Patients who present with a primary type 2 inflammatory disease should be asked about symptoms related to other type 2 inflammatory comorbid diseases (Table 1). Biomarkers, such as eosinophils and IgE in addition

to FeNO for asthma, should be used in the clinical assessment of the status of type 2 inflammation, and it would be useful to have validated biomarkers of type 2 inflammation relevant to atopic dermatitis.

Consensus was not achieved on whether, from the patient perspective, the combined symptoms related to multiple moderate type 2 inflammatory diseases may be more burdensome compared with the symptoms of a single severe type 2 inflammatory disease. At the virtual meeting, the experts highlighted that disease burden can be assessed only by the patient. In addition, patients with a single severe type 2 inflammatory disease may be eligible for effective treatments to alleviate their symptoms, which may not be available for patients with multiple moderately severe type 2 inflammatory diseases. Where clinical settings allow it, specialists should work together when managing patients with highly complex cases of multiple concurrent type 2 inflammatory diseases.

Although consensus was achieved regarding the most serious cases taking priority in multidisciplinary team conferences, it was not agreed that some patients with multiple concurrent, refractory, moderate type 2 inflammatory diseases may benefit from having their cases discussed in this setting. At the virtual meeting, the experts highlighted the cost of organising multidisciplinary team conferences as a potential barrier to these patients being discussed in this manner and said that patients with severe disease should be given priority.

Impact on the holistic care of patients with type 2 inflammatory diseases

In the dermatologists' breakout session, it was noted that some dermatologists in the Nordic region ask their patients about asthma but not about upper-airway symptoms or eosinophilic esophagitis. This is partly due to the limited time available for consultations but also stems from difficulties in assessing the severity of other comorbidities. A detailed knowledge of respiratory disease, for example, is not traditionally part of the dermatology specialty. It was noted that patient-reported outcome tools should be developed to assess the severity of comorbidities so that patients can be referred to an appropriate specialist. In addition, the importance of patient education to promote awareness of multi-organ disease was highlighted.

A key challenge highlighted by the dermatologists was the identification of patients with multi-organ disease even though patients may not mention non-dermatological comorbidities to their dermatologist. All participants agreed that a question guide would be useful to identify comorbidities proactively and facilitate appropriate holistic care for patients with type 2 inflammatory diseases.

Following the proposals in the dermatologists' breakout session, all specialties involved in this initiative contributed to the preliminary draft of a question guide (Table 4), intended as an indication of scope. It is anticipated that the questions would be rephrased in appropriate patient-friendly language and undergo validation with patient groups prior to clinical use.

In the pulmonologists and paediatricians' breakout session, it was noted that there may not be as much overlap between type 2 inflammatory diseases as the literature suggests. This may be because specialist clinics mostly see patients with severe and complex diseases, who are more likely to have type 2 inflammation-driven multi-organ disease, rather than patients who have milder disease(s). Ideally, a multidisciplinary team would discuss the optimal management and care of patients with type 2 inflammation-driven multi-organ disease, but the participants recognised the geographic and economic challenges associated with this approach.

In the breakout session that included the ENT, internal medicine, clinical immunology and allergy specialists, it was noted that patients with severe asthma and CRSwNP often experience overlapping symptoms. Therefore, the development of a composite score to holistically assess the severity of symptoms in patients with severe asthma and CRSwNP was recommended.

Discussion

Overall, there was general agreement that diseases associated with type 2 inflammation commonly coexist, although there is a lack of evidence to determine the extent of overlap in patients with three or more coexisting diseases. For some conditions, such as asthma with CRSwNP, there was agreement that coexisting type 2 inflammation-driven diseases may be associated with more severe disease. For patients with comorbid atopic dermatitis and asthma, the general perception is that their asthma will be mild, as demonstrated in the randomised, placebo-controlled phase 3 SOLO 1 and SOLO 2 studies of dupilumab in patients with atopic dermatitis.[33,49] However, in our clinical experience, patients with comorbid atopic dermatitis and asthma often have severe asthma. There is an urgent need for further understanding about the overall impact of the coexistence of type 2 inflammation-driven diseases on the total symptom burden in the individual patient. Such an understanding may also help to optimise patient management.

In this initiative, consensus on how and whether to use multidisciplinary team conferences to manage patients with coexisting type 2 inflammation-driven diseases was not reached. Although it was acknowledged that a holistic approach to identifying type 2 inflammation-driven comorbidities by a single healthcare provider would be ideal, it was recognised that the increasing specialisation of medicine would preclude this.

Given the frequent clinical coexistence of type 2 inflammation-driven diseases such as atopic dermatitis, asthma, chronic rhinitis, CRSwNP and eosinophilic esophagitis, it was agreed that there is a need for routine assessment of type 2 inflammation-driven diseases that are not routinely evaluated within each specialty. To provide an operational approach to screening patients, a short question guide was proposed for patients to complete in the waiting room prior to their consultation. The aim of the question guide is to aid clinicians from different specialties to recognise comorbidities and enable them to detect, address and refer appropriately. This may be an important tool to prevent deterioration of patients' health and improve their quality of life. Moreover, patient education may promote further awareness of the importance of addressing multi-organ disease. Both clinicians and patients need to be aware of the importance of the coexistence of multi-organ diseases driven by type 2 inflammation. In addition, our initiative highlighted the need for validated biomarkers of type 2 inflammation that are relevant to atopic dermatitis.

Atopic dermatitis lesions are primarily Th2 and Th22 skewed, with variable contributions of the Th1 and Th17 cytokine pathways depending on the disease subtype, including a particularly high activation of Th17 cytokine pathways in Asian patients compared with other ethnic populations.[50-54] Patients with chronic atopic dermatitis have a higher proportion of Th1 cells in the skin infiltrate compared with patients with acute atopic dermatitis.[55,56] It has been shown that patients with atopic dermatitis have significantly higher rates of autoimmune comorbidities (including autoimmune diseases of the skin, gastrointestinal tract and connective tissue) compared with healthy individuals.[57] These associated autoimmune diseases are likely not driven by type 2 inflammation, but there is a strong overlap in genetic risk alleles between autoimmune diseases and atopic dermatitis.[58-60]

This consensus approach was limited by the relatively low number of participants, and their geographic concentration (six Nordic countries) may limit the applicability of our recommendations in less-developed areas of the world. Additionally, the experts had diverse specialties and some of them did not necessarily have sufficient clinical experience with certain type 2 inflammation-driven diseases outside their area of expertise. The scope of our initiative did not include other type 2 inflammation-driven diseases such as eosinophilic chronic rhinosinusitis without nasal polyps.[61] In addition, the term 'chronic rhinitis' was used in this multidisciplinary modified Delphi consensus initiative because those who are not experts in otorhinolaryngology are generally unable to diagnose non-allergic rhinitis subsets or chronic rhinosinusitis without nasal polyps. However, we recognise that the term 'chronic rhinitis' may include some subsets that are not primarily driven by type 2 inflammation. Finally, although the modified Delphi process is an accepted methodology, it is based on expert opinion and is thus open to possible bias, particularly given the relatively low number of participants.

In conclusion, our initiative achieved a consensus definition of type 2 inflammation; characterised its role

as an immunopathological driver of asthma, atopic dermatitis, chronic rhinitis, CRSwNP and eosinophilic esophagitis; and reached consensus on the presence of overlap between these diseases. Further studies to characterise the overlap between the diseases are warranted. Our conclusions should be used as a framework to further understand the extent of type 2 inflammation-driven multi-organ disease and improve the holistic management and care for patients with type 2 inflammation-driven disease.

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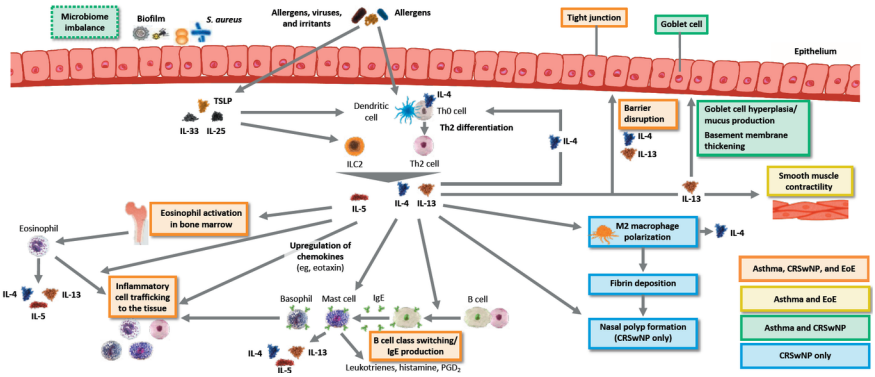
Figures

FIGURE 1. (A) Type 2 inflammation pathway; type 2 inflammation pathways in **(B)** asthma, **(C)** atopic dermatitis,**(D)** chronic rhinosinusitis with nasal polyps and **(E)**eosinophilic esophagitis

(A)



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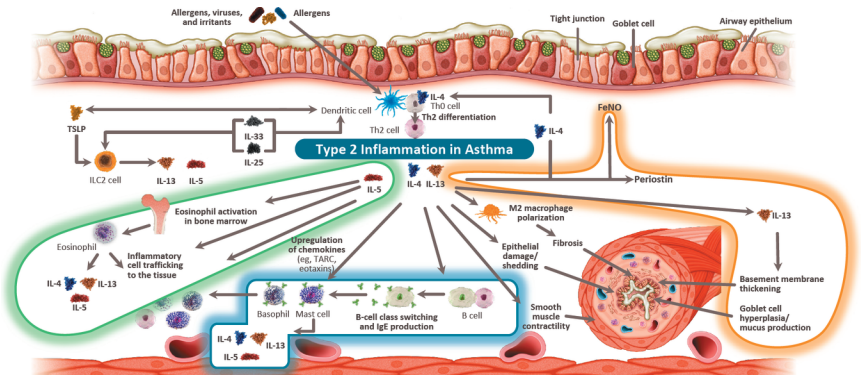
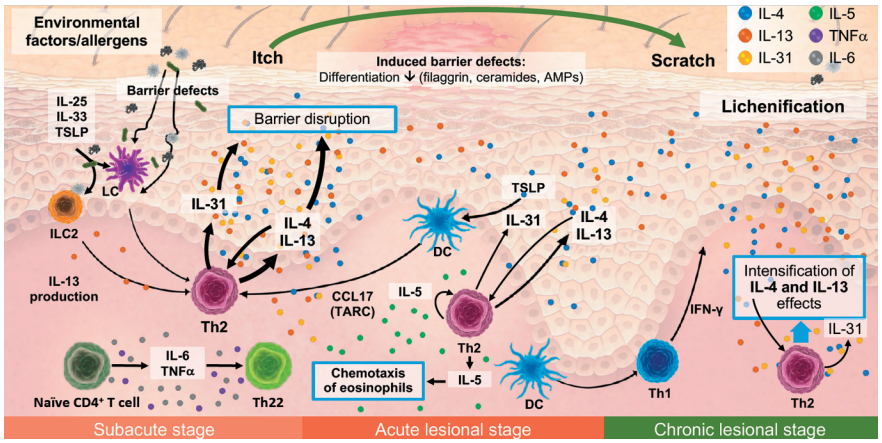


(C)*



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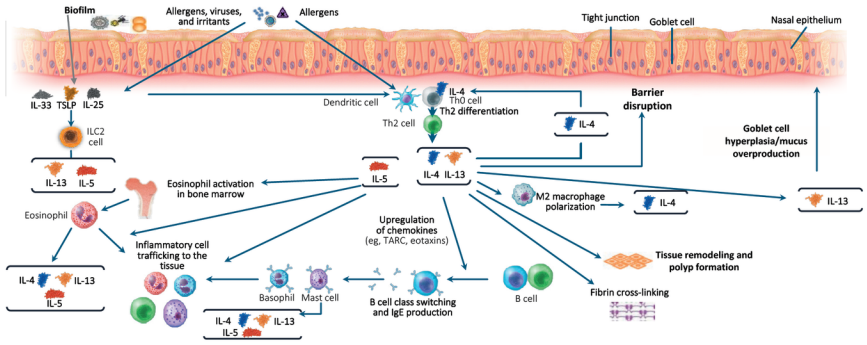
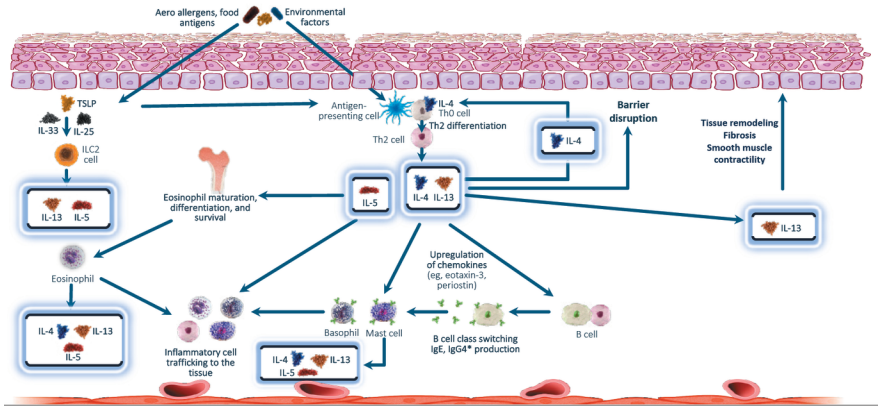


(E)



*Allergen exposure/penetration and initiation of alarmin activity occurs at the subacute, acute lesional and chronic lesional stages, but has only been illustrated at the subacute stage to improve readability. AMPs, antimicrobial peptides; CRSwNP, chronic rhinosinusitis with nasal polyps; DC, dendritic cell; EoE, eosinophilic esophagitis; FeNO, fractional exhaled nitric oxide; Ig, immunoglobulin; IL, interleukin; ILC2, type 2 innate lymphoid cell; PGD_2, prostaglandin D2; TARC, thymus- and activation-regulated chemokine; Th, T helper cell; TNFα, tumour necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

Figure 2. Modified Delphi process

Questionnaire responses were scored on a 9-point Likert scale (consensus: mean score [?]3 with [?]1 outlier; near consensus: mean score [?]3.5 with [?]2 outliers; no consensus: mean score >3.5 or [?]3 outliers). *The SC used the results of the literature search to design the Delphi questionnaire, which consisted of 23 consensus statements. Published work identified in the literature search that was relevant to each consensus statement was provided to all participating experts for context. $^{+}$Owing to expert feedback on the questionnaire, which noted that some experts felt that they were not fully qualified to answer some questions outside their specialty, a post hoc subgroup analysis stratified by relevant specialty(ies) was conducted to explore whether this affected the levels of consensus.$^{++}$Based on feedback from the experts, which excluded all statements that had achieved consensus in the first round. One statement was made optional so that experts could abstain from voting if they felt that they did not have relevant expertise. Seven statements included responses from experts within the dermatology subgroup, which included experts with specialist knowledge about dermatological diseases (allergists, clinical immunologists, dermatologists, internal medicine specialists and paediatricians), or the respiratory subgroup, which included experts with a high level of knowledge about respiratory diseases (allergists, clinical immunologists, ENT specialists, internal medicine specialists, paediatricians and pulmonologists).§The SC and experts gathered virtually on 22 October 2020 to review and discuss the conclusions from the Delphi questionnaires. The virtual meeting was facilitated by Keena McKillen on behalf of OPEN Health Medical Communications. The SC moderated breakout sessions where the experts discussed how the results of the Delphi questionnaires may impact the holistic care of patients with type 2 inflammatory diseases within their respective specialties.¶At the virtual meeting, a member of the SC, U.S. Björnsdóttir, provided insight into the role of type 2 inflammation as a driver of eosinophilic esophagitis. After reviewing all available evidence, it was agreed that the corresponding consensus statement should be re-circulated to the expert group and SC as a third-round questionnaire.

Tables

TABLE 1 Delphi consensus statements

Consensus statement	**Consensus status***	**Respondents**
For the purposes of simplification, the underlying immunopathology of type 2 inflammation can be considered as Th2 cell and/or ILC2 activation, with expression of type 2 inflammation cytokines, including interleukin (IL)-4, IL-5 and IL-13, and can often be characterised by the elevation of certain biomarkers, including (but not limited to) allergen-specific immunoglobulin (Ig)Es, elevated levels of blood and/or tissue eosinophils, and, in asthma, elevated fractional exhaled nitric oxide (FeNO).	Consensus (Second Delphi questionnaire)	All experts
Type 2 inflammation may be considered as an underlying immunopathological driver of some phenotypes of asthma.	Consensus (First Delphi questionnaire)	Respiratory subgroup
Type 2 inflammation may be considered as an underlying immunopathological driver of some types of chronic rhinitis.	Consensus (Second Delphi questionnaire)	Respiratory subgroup
Type 2 inflammation may be considered as an underlying immunopathological driver of chronic rhinosinusitis with nasal polyps.	Consensus (First Delphi questionnaire)	Respiratory subgroup
Type 2 inflammation may be considered as an underlying immunopathological driver of atopic dermatitis.	Consensus (First Delphi questionnaire)	Dermatology subgroup
Type 2 inflammation may be considered as an underlying immunopathological driver of eosinophilic esophagitis.	Consensus (Third Delphi questionnaire circulated after the virtual meeting)	All experts
Epidemiological evidence suggests that, in ADULTS, there is an overlap in the occurrence of asthma, chronic rhinitis with or without nasal polyps, atopic dermatitis and eosinophilic esophagitis.	Consensus (First Delphi questionnaire)	All experts
However, most of the epidemiological studies are too heterogeneous to draw accurate conclusions about the exact extent of the overlap. Therefore, more evidence is required.	Consensus (First Delphi questionnaire)	All experts

Consensus statement	Consensus status*	Respondents
Epidemiological evidence suggests that, in CHILDREN, there is an overlap in the occurrence of asthma, chronic rhinitis, atopic dermatitis and eosinophilic esophagitis.	Consensus (First Delphi questionnaire)	All experts
However, most of the epidemiological studies are too heterogeneous to draw accurate conclusions about the exact extent of the overlap. Therefore, more evidence is required.	Consensus (First Delphi questionnaire)	All experts
Atopic dermatitis and asthma can coexist in adults and children.	Consensus (First Delphi questionnaire)	All experts
Asthma and chronic rhinitis can coexist in some patients.	Consensus (First Delphi questionnaire)	All experts
Asthma and chronic rhinosinusitis with nasal polyps can coexist in some adult patients.	Consensus (First Delphi questionnaire)	All experts
Adult-onset asthma with chronic rhinosinusitis with nasal polyps is a distinct subset of asthma and presents clinically with a disease that is more difficult to control compared with other subsets of asthma	Consensus (First Delphi questionnaire)	Respiratory subgroup
In my clinical experience, the presence of more than one atopic condition such as asthma, chronic rhinitis, chronic rhinosinusitis with nasal polyps, atopic dermatitis and eosinophilic esophagitis may often predispose patients, especially adult patients, to more severe disease compared with having only a single atopic condition.	Consensus (Second Delphi questionnaire)	All experts
In my clinical experience, type 2 inflammation may drive mild, moderate and severe forms of asthma, chronic rhinitis, chronic rhinosinusitis with nasal polyps, atopic dermatitis and eosinophilic esophagitis.	Consensus (First Delphi questionnaire)	All experts

Consensus statement	Consensus status*	Respondents
In my clinical experience, some overlapping types of asthma, chronic rhinitis, chronic rhinosinusitis with nasal polyps, atopic dermatitis and eosinophilic esophagitis may be considered as a set of related multimorbid conditions driven by underlying type 2 inflammation.	Consensus (Second Delphi questionnaire)	All experts
Patients presenting with a primary type 2 inflammatory condition should be asked about symptoms related to other type 2 inflammatory comorbid conditions.	Consensus (First Delphi questionnaire)	All experts
Biomarkers, such as eosinophils, IgE and FeNO for asthma, should be used in the clinic to assess the status of type 2 inflammation.	Consensus (First Delphi questionnaire)	Respiratory subgroup
It would be useful to have validated biomarkers of type 2 inflammation relevant to atopic dermatitis.	Consensus (Second Delphi questionnaire)	Dermatology subgroup
Where clinical settings allow for this, specialists should work together across functions when managing patients with severe signs and symptoms of multiple concurrent type 2 inflammatory conditions.	Consensus (Second Delphi questionnaire)	All experts
Patients with a severe refractory type 2 inflammatory condition and additional type 2 inflammatory conditions will benefit from having their cases discussed at cross-functional multidisciplinary team conferences.	Consensus (First Delphi questionnaire)	All experts
The pattern of overlap in asthma, rhinitis, chronic rhinosinusitis with nasal polyps, atopic dermatitis and eosinophilic esophagitis, captured in previous statements, is reflective of my clinical experience.	Near consensus (Experts could abstain from voting)	All experts

Consensus statement	Consensus status*	Respondents
The pattern of overlap in asthma, rhinitis, chronic rhinosinusitis with nasal polyps and atopic dermatitis captured in previous statements, is reflective of my clinical experience.	No consensus	All experts
The combined symptoms related to multiple moderate type 2 inflammatory conditions may be more burdensome for a patient compared with the symptoms of a single severe type 2 inflammatory condition.	No consensus	All experts
While the most serious cases should take priority in cross-functional multidisciplinary team conferences, some patients with multiple concurrent refractory moderate type 2 inflammatory conditions may benefit from having their cases discussed in this setting.	No consensus	All experts

*The answers were scored on a 9-point Likert scale. Consensus: mean score [?]3 with [?]1 outlier. Near consensus: mean score [?]3.5 with [?]2 outliers. No consensus: mean score >3.5 or [?]3 outliers.

TABLE 2. Published epidemiological evidence of the overlap of type 2 inflammation-driven diseases in adults

Primary condition	Percentage of patients who also have asthma	Percentage of patients who also have atopic dermatitis	Percentage of patients who also have chronic rhinitis	Percentage of patients who also have CRSwNP	Percentage of patients who also have eosinophilic esophagitis
Adults with asthma		15.4–72.3% (data from 10 studies)[22,27,62-69]	14.0–95.0% (data from 17 studies)[22,26,27,62-68,70-76] 30.0–95.0% from 5 reviews[26,70,71,73,75]	9.0–44.0% (data from 5 studies)[67,74-77] 9.0% from 1 review[75]	–
Adults with atopic dermatitis	6.3–44.4% (data from 11 studies)[2,26,63,69,78-84] 8.0–43.0% from 5 reviews[2,26,79,82,83]		8.0–75.0% (data from 7 studies)[2,26,63,79-81,83] 8.0–75.0% from 3 reviews[2,79,83]	1.2–14.8% (data from 4 studies)[85-89]	–

Primary condition	Percentage of patients who also have asthma	Percentage of patients who also have atopic dermatitis	Percentage of patients who also have chronic rhinitis	Percentage of patients who also have CRSwNP	Percentage of patients who also have eosinophilic esophagitis
Adults with chronic rhinitis	10.0–55.0% (data from 12 studies)[17,24,26,70,73,75,80,90,94] 10.0–50.0% from 6 reviews[26,70,71,75,80,91]	8.8–15.4% (data from 2 studies)[17,94]		8.9% (data from 1 study)[24]	–
Adults with CRSwNP	23.9–58.3% (data from 4 studies)[21,25,75,95] 50.0% from 1 review[75]	4.2–16.5% (data from 3 studies)[21,25,95]	42.7–56.7% (data from 3 studies)[21,25,95]		–
Adults with eosinophilic esophagitis	12.0–84.0% (data from 9 studies)[18,19,83,96-101] 12.0–84.0% from 5 reviews[19,83,97-99]	4.0%–55.0% (data from 7 studies)[18,19,83,96,98,100,101] 4.0–55.0% from 3 reviews[19,83,98]	30.0–93.0% (data from 7 studies)[18,19,83,96,97,100,101] 30.0–93.0% from 3 reviews[19,83,97]	–	

CRSwNP, chronic rhinosinusitis with nasal polyps.

TABLE 3. Published epidemiological evidence of the overlap of type 2 inflammation-driven diseases in children

Primary condition

Percentage of patients who also have asthma

Percentage of patients who also have atopic dermatitis

Percentage of patients who also have chronic rhinitis

Percentage of patients

who also have

eosinophilic esophagitis

Children with asthma

24.0% (data from 1 study)[102]

Hazard ratio: 1.7 and 40.0% (data from 2 studies)[102,103]

Hazard ratio: 1.9 and 13.0% (data from 2 studies)[103,104]

Children with atopic dermatitis

13.1–36.0% (data from 10 studies)[22,68,78,84,93,103,105-108] 26.3–35.8% from 2 reviews[84,106]

4.0–61.0% (data from 6 studies)[22,68,78,93,102,103]

Hazard ratio: 3.2 (data from 1 study)[103]

Children with chronic rhinitis

24.7–59.0% (data from 4 studies)[22,63,68,102]

4.0–53% (data from 4 studies)[22,63,68,102]

Hazard ratio: 2.8 (data from 1 study)[103]

Children with eosinophilic esophagitis

45.4–59.8% (data from 3 studies)[96,109,110]

17.8–46.4% (data from 3 studies)[96,109,110]

60.3–64.0% (data from 2 studies)[96,109]

TABLE 4. Question guide to identify possible type 2 inflammation-driven comorbidities

Adult patients
Are you experiencing anosmia/nasal congestion or discharge/facial pressure or pain?
Are you experiencing flares of eczema or itching?
Are you experiencing dysphagia/food impaction?
Are you experiencing cough/wheezing/shortness of breath or chest tightness either in rest or provoked by activity?
Paediatric patients
Does the child cough when playing/laughing/running or while asleep?
Does the child have dry skin/eczema/itching?
Does the child show signs of failure to thrive (small children) or dysphagia/anorexia/vomiting after food intake (older child
Does the child have allergies?
Does the child withdraw easily from energetic playing/laughing/running?