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EUFOREUM Berlin 2023: Optimizing care for type 2 inflammatory diseases from clinic to AI: A pediatric focus

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Abstract

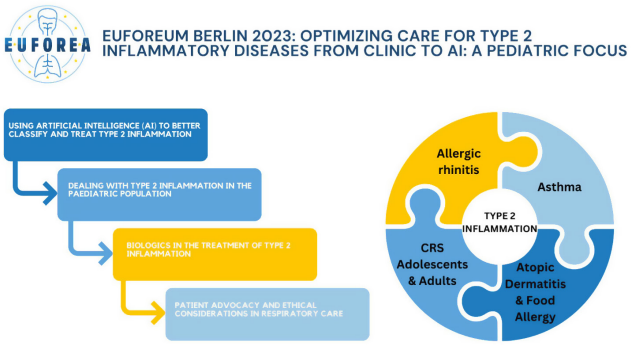
The European Forum for Research and Education in Allergy and Airways diseases (EUFOREA) organized its bi-annual forum *EUFOREUM* in Berlin in November 2023. The aim of *EUFOREUM* 2023 was to highlight pediatric action plans for prevention and optimizing care for type 2 inflammatory conditions starting in childhood, with a focus on early-stage diagnosis, ensuring neither under- nor overdiagnosis, optimal care, and suggestions for improvement of care. EUFOREA is an international not-for-profit organization forming an alliance of all stakeholders dedicated to reducing the prevalence and burden of chronic respiratory diseases through the implementation of optimal patient care via educational, research, and advocacy activities. The inclusive and multidisciplinary approach of EUFOREA was reflected in the keynote lectures and faculty of the virtual *EUFOREUM* 2023 (www.euforea.eu/euforeum) coming from the pediatric, allergology, pulmonology, ENT, dermatology, primary health care fields and patients around the central theme of type 2 inflammation. As most type 2 inflammatory conditions may start in childhood or adolescence, and most children have type 2 inflammation when suffering from a respiratory or skin disease, the moment has come to raise the bar of ambitions of care, including prevention, remission and disease modification at an early stage. The current report provides a comprehensive overview of key statements by the faculty of the EUFOREUM 2023 and the ambitions

Abbreviations: AERD, Aspirin-exacerbated respiratory disease; AI, Artificial intelligence; AIT, Allergen immunotherapy; AR, Allergic rhinitis; COPD, Chronic obstructive pulmonary disease; CRS, Chronic rhinosinusitis; CRSwNP, Chronic rhinosinusitis with nasal polyps; CSU, Chronic spontaneous urticaria; EAACI, European Academy of Allergy & Clinical Immunology; EFA, European federation of allergy and airways diseases; EoE, Eosinophilic esophagitis; ERS, European respiratory society; EUFOREA, European forum for research and education in allergy and airways diseases; ICS, Inhaled corticosteroids; NCS, Nasal congestion score; NPS, Nasal polyp score; QoL, Quality of life; RSV, Respiratory syncytial virus; SCIT, Subcutaneous immunotherapy; SLIT, Sublingual immunotherapy; SNOT-22, Sino-nasal outcome test.

For affiliations refer to page 10.

of EUFOREA allowing all stakeholders in the respiratory field to be updated and ready to join forces in Europe and beyond.

KEYWORDS
AD, allergic rhinitis, asthma, EUFOREA, pediatrics, rhinosinusitis, T2-inflammation



GRAPHICAL ABSTRACT
The contents of this page will be used as part of the graphical abstract of html only. It will not be published as part of main article.

1 | INTRODUCTION

Chronic airways and allergic diseases are widespread health concerns that affect millions of people worldwide, not least in westernized society where they have reached epidemic proportions.[1] Conditions driven by type 2 inflammation such as asthma, allergic rhinitis (AR), chronic spontaneous urticaria (CSU), and chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) can cause significant morbidity, reduced quality of life, and increased healthcare costs.[2] The prevalence of type 2-driven inflammatory conditions has risen globally. Several of these diseases start in childhood or adolescence presenting opportunities for timely treatment with the aim of achieving control and even remission.[3] Therefore, researchers, clinicians, and patients need to better understand type 2 inflammation, to address both major unmet needs and arrest or retard disease progress before an irreversible chronic status is reached[4] (Table 1).

EUFOREA is an international non-profit organization founded in 2015 on the suggestion of the European Commissioner of Health Vytenis Andriukaitis, forming an alliance of multiple stakeholders dedicated to reducing the prevalence and burden of chronic respiratory diseases through the implementation of optimal patient care via educational, research, and advocacy activities. The following problems have been recognized as obstacles for the improvement of care and prevention: (i) lack of structural collaboration between larger and smaller organizations with a focus on only one segment of the respiratory tract, (ii) lack of focus on prevention and optimal care by most scientific organizations, (iii) lack of true collaboration between specialists from different disciplines in the respiratory field, (iv) lack of joint advocacy initiatives on having patients' voices heard in Europe and beyond, and (v) lack of a truly global patient advisory board of patients suffering from long-term chronic respiratory diseases.[5]

Key message

The current report provides a comprehensive overview of key statements by the faculty of the EUFOREUM 2023 and the ambitions of EUFOREA allowing all stakeholders in the respiratory field to be updated and ready to join forces in Europe and beyond.

Based on EUFOREA's core values of inclusivity and innovation, the *EUFOREUM* 2023 was organized with the ambition to bring to the attention of a large and global audience state-of-the-art knowledge on type 2 inflammation in childhood and adolescence with a focus on unmet needs, optimal care, and novel treatment targets, including remission and prevention. The collaboration between primary care physicians, pulmonologists, allergologists, ENT surgeons, pediatricians, dermatologists, and patient advocates reflects the ambition of EUFOREA to be inclusive and multidisciplinary (Figure 1). EUFOREA aims not only to promote innovation in the diagnosis, treatment, and management of chronic respiratory diseases and allergie but also to advocate for policies and regulatory bodies dealing with respiratory health.[6]

The 2023 *EUFOREUM* reunited 19 well-recognized global experts to present a total of 18 lectures and three training courses on anaphylaxis, asthma, and allergen immunotherapy (AIT). The meeting aimed to train specialists in type 2 inflammation with a

TABLE 1 Epidemiological and immunopathogenic considerations in pediatric Th2 diseases.

Epidemiological and immunopathogenic considerations in pediatric Th2 diseases

Disease	Epidemiological estimation	Burden in the pediatric age
Asthma	9.1%–13.6%[102,103]	Asthma is one of the main causes of hospitalization which are particularly common in children aged <5 years[104,105]
		Indirect costs are usually higher than in older patients, including both school and work-related losses[104,105]
		Intangible costs are unquantifiable, since they are related to impairment of quality of life, limitation of physical activities, and study performance[104,105]
Allergic rhinitis	8.39%–19.87%[106,107]	Children with nasal allergies were significantly less likely to receive an excellent health rating by their parents than were children without allergies[108,109]
		Pediatric AR interferes with children's performance at school[108,109]
		Parents' reports of decreased productivity, difficulty in completing tasks, and reduced amount of time spent on daily activities resulted in reductions in what the child with nasal allergies was perceived to accomplish on a daily basis[108,109]
		Nasal obstruction or congestion, such as occurs with AR, is associated with a disruption in the normal pattern of breathing in adults[108,109]
		Comorbid conditions occurring with AR include eye symptoms, such as conjunctivitis, ear problems (otitis), headaches, sinusitis, snoring, and dental issues, such as malocclusion[108,109]
Acute urticaria	2.1%–6.7%[110,111]	Impact on patients' QoL with significant consequences reported on sleep, social interactions, and work performance[112–115]
		Individuals suffering from chronic urticaria may develop mental health problems over time, with anxiety and depression reported in more than 30% of patients[112–115]
Chronic spontaneous urticaria	0.1% up to 3%[116]	The economic burden of urticaria considers medication costs and absenteeism[112–115]
Angioedema	1.7%–1.9%[117,118]	The burden of disease for patients with HAE is substantial. Attacks are unpredictable with respect to frequency, severity, and the site that swells. Laryngeal attacks can be fatal if not treated promptly and appropriately[117–119]
		Feelings of stress, anxiety, and depression can trigger attacks, and begin a cycle of attacks that cause anxiety that, in turn, triggers further attacks[117–119]
		Despite full physical recovery between attacks, patients often experience continual emotional impairment and reduced quality of life[117–119]

special focus on childhood and adolescence, to place the patient at the center of the medical consultation, addressing a broad spectrum of pathology, proposing rational therapeutic options, and using targeted practical tools. It was based on three learning objectives: to gain insight into innovative approaches and optimal care for asthma, allergies in children and adults, and CRS in adolescents and young adults; to learn about relevant endotypes and phenotypes in chronic respiratory diseases; and to understand unmet needs in the respiratory domain. Furthermore, as atopic diseases often commence in infancy with atopic dermatitis and/or food allergy, lectures also included skin manifestations such as atopic eczema as non-respiratory manifestations of type 2-driven or IgE-driven diseases. As an additional topic chronic urticaria as an own entity was also included.

The *EUROREUM* increased and highlighted the need for a multidisciplinary approach to T2-driven diseases and their complications. Overall, the discussions underscored the need for increased attention and resources in research, education, and advocacy to address unmet needs and promote positive change in various areas. The full content of the *EUFOREUM* 2023 is available on the EUFOREA website under the e-Academy section.

2 | USING ARTIFICIAL INTELLIGENCE (AI) TO BETTER CLASSIFY AND TREAT TYPE 2 INFLAMMATION

By 2015, it was made clear that precision medicine was a necessity and something from which patients could benefit, with advocacy events organized in the European Parliament by EUFOREA, ERS, and the European Academy of Allergy and Clinical Immunology (EAACI).[7,8] Efforts to move forward in the field of precision

FIGURE 1 Two chairs and hosts of the *EUFOREUM* 2023, Professor Susanne Lau and Professor Ulrich Wahn, surrounded by part of the faculty (From left to right: Prof. Peter Hellings, Katie Tassell, Prof. Susanne Lau, Prof. Ulrich Wahn, Dr. Dermot Ryan, and Prof. Vibeke Backer).

medicine encompass pharmacovigilance, medical registries of real-world efficacy data, randomized controlled trials, and observational studies, among others.[9] The recent incorporation of AI is a potential additional tool to achieve better care, however, still unproven.[10] This new capability to generate clusters of information and patients that can be split, grouped, and analyzed expands therapeutic possibilities. With the proposal of the European Health Data Space in April 2022, EFA (the European Federation of Allergy and Airways Diseases) became a key stakeholder in discussions with policymakers, reinforcing patients' rights to privacy and access to justice, the importance of health data for research and innovation, as well as patients' concern for security and privacy, due to the sensitivity of health data.

The first studies of AI applied to medicine are already available. Recently, Kaplan et al. established comparisons between the performance of AI versus that of medical specialists in diagnostic studies, and in some cases, the results are encouraging.[11] Wearables in healthcare are already a reality and commercial watches are capable of measuring parameters such as sleep, heart rate, blood pressure, blood oxygen, blood glucose, and body temperature and can send reminders about time spent sitting or time without drinking water. Clearly, there is room for improvement in accuracy, but having an app on your phone to receive and archive your own metrics is now part of many patients' digital fingerprint.[12]

AI might help eliminate subjectivity for outcome assessment and could become another tool in the medical toolbox, without replacing the professional judgment of a qualified physician. Above all, medicine is an art that needs science and a science that needs art. AI is just a part of but will not replace human contact and the patient-doctor relationship based on mutual trust in the approach and delivery of treatment. Hopefully in the future when AI is an assistant in the consultation, it will free up time for doctors to spend on supporting and meeting patients' needs but we very much need to be aware of potential biases within AI and the adverse effects already obvious in the consultation.[13]

Patient characterization provides clinicians and patients with a unique opportunity for individualized treatment. Over the last 50 years, there has been an elucidation of the inflammatory nature and pathophysiology of different types of asthma.[14] Several epidemiological cohorts and longitudinal studies have been conducted. Moreover, there has been a shift from clinical symptoms and histopathology to genetics, epigenetics, omics, personalized medicine, as well as AI, BIG data, and real-world data. In this respect, two main strands have recently been proposed. The microbiome has emerged as one of the proposed factors in the development of asthma. This is explained by the low diversity of the immune system instruction (atopy), combined with airway hyperresponsiveness and epithelial dysregulation.[15] The current direction of asthma research addresses also airway epithelial cells and how their genes are regulated. This includes the evaluation of bacteria in the airways of patients with asthma compared to those without asthma but also mucus and its impact on inflammation.[16] The question that remains unanswered is whether different bacteria play a role in the development of certain types of asthma and whether the dysbiosis on the airway epithelium could be a target in the future. Associations between the gut microbiome and severity of asthma are reported.[17] Gene editing of the microbiome could be a promising area for exploration.[18,19] Furthermore, proteins of epithelial cells like CC16 from club cells may serve as a biomarker predicting the likelihood of exacerbation of asthma.[20]

3 | DEALING WITH TYPE 2 INFLAMMATION IN THE PEDIATRIC POPULATION

Depending on environmental exposure, diet, and genes, allergies affect approximately one-third of the overall population, with AR affecting one-fifth, atopic dermatitis 10%, and asthma, and food allergy at 5% in younger age groups.[21–24] All these diseases have a multifactorial cause depending on genetic and epigenetic conditions and environmental exposure including diet. The early origin of allergic respiratory diseases, atopic dermatitis, and food allergy in a majority of patients who may still suffer from these diseases in adulthood leads to the question of whether better detection of at-risk children may have an impact on prevention and disease modification. Until now, atopic family history, early severe atopic dermatitis, and early sensitization to aeroallergens are major risk factors for later asthma.[25–27] However, this represents only a subgroup of children who will develop asthma and good biomarkers are still lacking in terms of asthma prediction in general. In a subgroup of patient's genetic markers help to predict severity[28] or comorbidity.[29] Knowing that lifestyle factors and the exposome[30–34] are key factors regarding epigenetics and activating and silencing of genes, the environment is a target for prevention.[30–34] However, given the complexity, apart from general recommendations like avoidance of tobacco smoke exposure,[35] control of pollution and the beneficial environment of a farming community and/or dog keeping,[24,30] no clear preventive strategies are available for the prevention of allergic airway disease and asthma in childhood. In contrast, a clear recommendation for early feeding of complementary food (peanut) is given for children at risk for early peanut allergy with atopic dermatitis in countries with high prevalence of peanut allergy and high exposure.[36] Detection of pre-asthma is the subject of a further EUFOREA paper.[37]

AR has a substantial effect on quality of life, and school performance, and increases the risk of bronchial hyperreactivity and asthma development, attention deficit and hyperactivity disorders, chronic fatigue syndrome, headaches, and respiratory tract infections.[38] Viral respiratory infections also serve as one of the most significant triggers for exacerbations of allergic symptoms and additional nasal symptoms. There is an increase in the prevalence of AR and bronchial asthma, accompanied by lower age of presentation. This is evidenced by the classical clinical manifestations of both conditions, which are becoming more common in lower age categories.[39] It is not just respiratory tract allergies that are prevalent, but also comorbidities that significantly impact the quality of life.[40] These conditions may remain untreated, inappropriately treated, or inadequately managed, allowing the progression of sensitization, which represents a loss of opportunity to effectively stop the development of allergies and worsening symptoms.[14]

The prevalence of type 2 inflammation in childhood is significant.[14,41] This phenotype is observed in all age groups, including children under 3 years old who exhibit wheezing in relation to asthma progression.[14] Before classifying children as asthmatic or severely asthmatic, it is essential to exclude factors such as non-adherence, persistent exposure to allergens, inappropriate inhalation techniques, incorrect diagnosis, and co-morbidities and their impact on their quality of life. EUFOREA and the European Respiratory Society (ERS) endorse the use of objective diagnostic tools to prevent under- and overdiagnosis.[14] Inadequate endotyping in preschool wheezing/asthma, absence of predictors aside from family history, tobacco exposure, non-measurement of specific IgE, early atopic dermatitis and eosinophilia, lack of biologicals and therapeutic options for neutrophilic inflammation, the dangers of overuse of inhaled corticosteroids (ICS) in preschool children with a lack of control, and environmental threats such as pollution, climate change, and tobacco exposure are just some of the challenges in dealing with this reality.[14]

Upper and lower airways share a common environment where eosinophils and Type 2 mediators are present. Biomarkers which are available today may help to make the global airways concept more understandable for clinicians[42] (Figure 2). To manage the patient's care comprehensively, a multidisciplinary approach involving all care providers is essential, where specialists practice collaboratively to control co-morbidities such as eczema, AR, or CRS in asthma patients.[43]

Prevention is essential, although there are still limitations. Identifying children with ongoing diseases and treating them promptly may prevent the natural course of the inflammatory mechanism and lead to better outcomes.[44] Specific AIT is a valuable tool against AR and may help achieve asthma remission in certain subgroups.[45–47] AIT has several beneficial aspects for patients. The potential healing effect or at least the clear decrease of symptom load on pre-existing symptoms, prevention before symptoms worsen, prevention against new sensitizations, and against the development of bronchial asthma are just a few of them.[38] AIT has the potential to modify the immune system, providing patients with a long-term effect, strengthening the epithelial barrier and leading to disease modification. For patients seeking long-term relief or a cure for their current disease, this treatment is the only effective option throughout the course of the disease[39] in those patients where allergens like pollen or house dust mite play a role for which AIT is available and

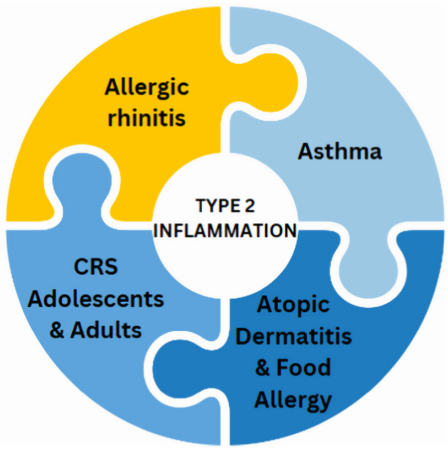


FIGURE 2 Common understanding in pediatric and adolescent Type 2 inflammation.

proven to be effective. AIT is the only treatment in the respiratory area which is a modifier, which can reduce the number of other allergies developed and furthermore, more severe disease to develop such as asthma. In contrast, both nasal steroid and inhaled steroid are controllers of the upper and lower airways, and beta2-agnostis in asthma is a reliever treatment.[39] Both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) have been shown to provide efficient treatment and alleviate symptoms for seasonal and perennial rhinitis and/or conjunctivitis[45] and pollen or HDM-induced bronchial asthma.[19] AIT is able to prevent more severe disease like asthma to develop in pollen allergic children with AR[19,39,45] and may prevent also new sensitizations.[19,39,45] SLIT and SCIT have high safety profiles, (in favor of SLIT), and provide long-term efficacy and the ability to prevent progression to asthma.[48,49] However, the clinical documentation of different AIT products is heterogeneous so that products should be evaluated individually regarding their clinical efficacy and safety profile. Only registered products with proven clinical efficacy and safety in double-blind controlled clinical trials should be used for AIT treatment.[50,51] Increasing patient, physician, and provider education could be accomplished in the foreseeable future and would result in significant benefits for patients (Table 2), although there are significant barriers to be overcome.[52]

Bronchial asthma poses new challenges and aims, such as the age of the patient at intervention, the course of the disease, and its structural changes. Early interventions are necessary to halt disease progression, potentially achieve disease remission, improve quality of life, improve lung function, and reverse remodeling changes.[53] The aims of management of bronchial asthma have progressed from mere symptom suppression to preventing exacerbations, to achieving disease control, and now to disease remission, which is characterized by a high level of disease control for a period of at least 1 year, with complete or partial absence of symptoms, complete absence of exacerbations, with or without ongoing treatment.[14]

Symptom control and prevention remain the best therapeutic approach, a goal that has not been easy to reach in early childhood, where viral infections are the major drivers for lower respiratory tract infections and wheezing. The immunization of pregnant women and /or young children against the respiratory syncytial virus (RSV)[54,55] may have a preventive impact in the future. Furthermore, the potentially disease-modifying effect of early use of biologics in children aged 6 months or older[9,56] with severe AD has to be studied.[57] The use of bacterial lysates in children with recurrent wheezing in preschool age has been proposed[58,59] and may potentially also have an impact on established asthma with recurrent viral-induced exacerbations. In order to identify children at risk for type 2-driven disease a proper screening by general practitioners and/or pediatricians trained in identifying compatible symptomatology at an early stage is key for implementing diagnostic and therapeutic steps as early as possible for an optimal outcome. Maybe, improved biomarkers will help us to predict better the risk of multi- or comorbidity to better implement early prevention strategies in especially vulnerable subgroups.

Early intervention may be favoring better disease control and remission, especially in groups with associated comorbidities. There is still lack of evidence and longitudinal studies are urgently needed especially in younger preschool children. One question for consideration in the future is when to initiate the most appropriate treatment to prevent disease progression, as discussed by Hamelmann et al.[60]

4 | BIOLOGICS IN THE TREATMENT OF TYPE 2 INFLAMMATION

Biological therapies are a useful treatment for various immune-mediated inflammatory diseases of the airways, such as asthma,[61,62] atopic dermatitis,[63] CSU,[64] and CRS, in which dysregulation of pathways are implicated.[65] These therapies are designed to selectively inhibit cytokines, resulting in a more targeted and precise treatment approach[66] than traditional therapies for type 2 inflammatory diseases, such as corticosteroids which have the major disadvantage of broad systemic effects which can lead to significant side effects.[67]

TABLE 2 Therapy in pediatric Type 2 inflammation.

Therapy in pediatric Type 2 inflammation

Biologics	AIT
Limited persisting effect after the end of treatment	Long-term effect
Disease remission on treatment	Disease modification
Disease modification to be demonstrated	
Limited use due to the inclusion criteria	Prevention before worsening of the symptoms/comorbidities
Not indicated alone in AR	Good results in AR/AC
	Good results in HDM-asthma
	Prevention of new sensibilizations
	Can be combined with biologics

In contrast, biologic treatments, being more targeted have reduced adverse events.[68] Biologic use is increasing, despite its costs, due to the ability to treat the underlying disease and its comorbidities concurrently.[69,70]

Since the latest generation of therapeutic regimens for asthma was introduced, the aim has been to achieve minimal or no symptoms while preserving physical activity, maintaining or improving lung function, preventing exacerbations, and avoiding systemic steroids while minimizing adverse effects and preventing disease progression.[61,62,71,72] Since the emergence of biologics as an alternative, this perspective has evolved, beginning with the suppression of symptoms, then the prevention of exacerbations, then the achievement of disease control, and currently disease remission, meaning symptom-free periods longer than 12 months under therapy.[57,71,73]

The use of biologics is helping us to better understand the pathophysiology of type 2 diseases. Response to them can also give us insight into the mechanisms involved in the disease or its comorbidities.[70] A disease has different subtypes and endotypes, and depending on who responds, we learn about the mechanisms that drive the condition, and that is also beneficial for patients. Endotyping is part of the new focus of precision medicine, which helps us understand that asthma is a heterogeneous disease driven by various inflammatory pathways, rather than a single disease.[70,74]

The mechanisms of action and indications for use of biologics may differ depending on disease severity and the comorbidities present in each patient (Table 3). Perhaps the most important aspect of managing pediatric asthma is utilizing biomarkers to guide treatment decisions, applying the appropriate treatment schema based on the patient's endotype, evaluating the use of biologics, and striving for disease remission.[14]

CSU differs from typical atopic T2-driven diseases mentioned before. Most urticaria in children is not allergic, but related to intercurrent viral infections and is transient.[75] In many patients, self-reactive IgE and autoantibodies to IgE or its high-affinity receptor, FceRI, play a major role. Thus, anti-IgE has become a major player in the treatment of antihistamine-resistant cases of CSU. The introduction of biologics has represented a significant addition to the therapeutic armamentarium, which was previously based on H1-antihistamines.[76] Due to its mast cell-mediated essence, different biologics emerged with mechanisms such as inhibition of mediators, inhibition of activation, silencing, or depletion.[77–79] Studies are being conducted to better elucidate the full spectrum of options.[80]

Atopic dermatitis is a common inflammatory skin disorder in all age and ethnic groups; however, the highest incidence is found in early infancy. The majority of young children have a mild course of the disease, although itching and impairment of sleep and quality of life can occur at any stage. The remission rate of early atopic dermatitis (or atopic eczema) is high, however, a substantial percentage have a relapsing and chronic course of AD. If topical anti-inflammatory treatment is insufficient for symptom control, systemic treatment options have become available for almost all age groups.

AD is the earliest manifestation of atopic disease, however, not all individuals with later allergic airway disease had signs of AD in

TABLE 3 Latest therapeutic agents with their age-related license.

Biologics and their applications					
Molecule	**Target**	**Application**	**Dose**	**Age indications**	**Indications**	**Other approved indications**
Omelizumab	IgE	SC/2–4 weeks	Body weight and pre-TH total IgE	≥6 years	Severe persistent allergic asthma/ inadequately controlled on high dose ICS + LABA	CSU ≥12 years/CRSwNP ≥18 years
Mepolizumab	IL-5	SC/4 weeks	Children 6–11 years 40 mg/≥12 years 100 mg	≥6 years	Severe eosinophilic asthma	CRSwNP & HES ≥18 years/EGPA ≥6 years
Reslizumab	IL-5	IV/4 weeks	Body weight 3 mg/kg	≥18 years (data for ≥12 years)	Severe eosinophilic asthma	
Benralizumab	IL-5Rα	SC/4–8 weeks	30 mg	≥18 years (data for ≥12 years)	Severe eosinophilic asthma	
Dupilumab	IL-4Rα/IL-13	SC/2 weeks	Loading 600 mg/ maintenance dose 300 mg	≥6 years for severe type 2 asthma ≥6 months for severe atopic dermatitis	Severe type 2 asthma inadequately controlled	AD ≥6 months/CRSwNP & EoE ≥18 years
Tezepelumab	TSLP	SC/2 weeks	210 mg	≥12 years	Severe asthma	

early infancy or childhood. Young patients with severe AD often develop food allergy and other atopic comorbidities and may follow the so-called "atopic march", especially if early and multiple sensitizations are present[81] (Figure 3). Whether early successful systemic treatment could modify the so-called atopic march remains unclear, however, it is worthy of further investigation. The pathophysiology of atopic dermatitis/atopic eczema is multifactorial, including genetic and epigenetic factors, epidermal barrier dysfunction, the skin and gut microbiome, and last but not least the type 2-predominant inflammation, mainly the involvement of IL4 and IL13, two cytokines promoting Th-cell differentiation into Th2 cells and IgE class switching into B-cells.[82] IL4 and IL13 both bind to the alpha subunit of the IL4 receptor. Thus, the development of monoclonal antibodies blocking IL4-R-alpha was a convincing new therapeutic approach in treating type 2 inflammation in AD.[83] Since March 2023, dupilumab as a blocking antibody of the IL4-R-alpha has also been licensed for infants and very young children with severe atopic dermatitis from 6 months on. For adolescents, it was already licensed in 2019, so a phase of 4 years of treating patients under 18 years of age with moderate to severe AD can be overviewed in terms of efficacy and side effects.[58,82–86] Fortunately, the treatment is well tolerated and safe; approximately 5% of adolescent patients encounter milder side effects like conjunctivitis, facial redness, and eosinophilia. In parallel, monoclonal antibodies to IL13 (tralokinumab) and JAK inhibitors (upadacitinib) were licensed for moderate to severe AD in adolescents (≥12 years) and adults.[87,88] Baricitinib, a JAK1 and 2 inhibitor is another systemic treatment option in very young children (≥2 years) with moderate to severe AD. As dupilumab is also licensed for severe asthma from age 6 years on, it provides an attractive therapeutic option for patients with multiple type 2-driven comorbidities. A rare manifestation oftype 2- and eosinophilic-driven disease is eosinophilic esophagitis (EoE), where dupilumab is also licensed from 12 years (≥40 kg) upwards.

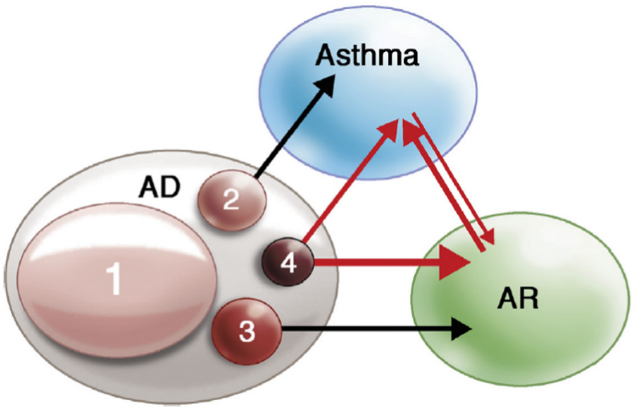


FIGURE 3 Potential trajectories of disease progression toward asthma and AR in patients with AD initially (the atopic march). Extracted from Paller AS 2019 with permission.[101] Different shades of pink/red/maroon represent different AD endotypes. The majority of patients with AD do not have either of these atopic comorbidities (1). The subsets of patients at highest risk for the atopic march to asthma (2), AR (3), or both (4) tend to have more severe persistent disease, early sensitization, and a family history of atopy. Although it is most common for AD to be the first component of the atopic march, AD can also follow the development of asthma or AR. FA also occurs frequently in children with AD and not infrequently precedes AD.

CRS is a heterogeneous disease characterized by local inflammation of the upper airways and sinuses that persists for at least 12 weeks. CRS can be divided into two phenotypes, dependent on the presence of nasal polyps, namely CRSwNP and CRS without nasal polyps (CRSsNP). Severe and recalcitrant CRSwNP in adults has been effectively managed using biologics for several years. The incorporation of these medications in recent treatment guidelines has brought about significant changes in patient management.[89] Incorporating dupilumab in the treatment regime has demonstrated a decrease in nasal polyp scores (NPS) and the patient's burden related to quality of life (QoL).[90] Mepolizumab has also demonstrated a reduction in the likelihood of requiring nasal surgery as part of the treatment regimen and has been shown to be effective in patients with associated comorbidities such as asthma or aspirin-exacerbated respiratory disease (AERD).[91] The efficacy of Omalizumab has been evaluated and verified through the NPS, nasal congestion score (NCS), and sino-nasal outcome test (SNOT-22) scores.[92] The release of the most recent EUFOREA guidelines for defining and treating CRSwNP, including the criteria for administering biologics to patients, has been a crucial and widely referenced development.[70] Clinical control, a state in which patients exhibit no symptoms or experience no detrimental effects on their quality of life, is a realistic goal in this disease.[70]

The question of biologics to treat severe AR is different. Biologicals are much more expensive than other available treatment alternatives and do not offer comparable results.[93] Omalizumab has demonstrated similar results to nasal sprays and was found to be effective only in patients with associated asthma.[57] No biological has provided evidence of disease modification, although its combination with other therapeutic options, such as AIT, has shown synergy and better outcomes in some cases.[94] However, the high costs have made biologic treatment almost inaccessible. Therefore, biologics may only play a role in treating AR, if they become more accessible; and only as part of a combined treatment.[95]

Considering biologics at a younger age is increasingly discussed. The current criteria to start biologics in very young patients is restrictive and aimed at treating patients with severe disease rather than preventing them from developing severe disease.[57,63,71,72] It is crucial that we diagnose early, endotype, and use the appropriate tool at the correct moment. One argument against biologics is their cost, but we must also consider the associated costs of cheaper alternative treatments such as corticosteroids incurred through the development of treatment-related impaired growth velocity in children, osteoporosis, diabetes, cataracts, obesity, OSA, and depression. It may be possible to significantly reduce lifetime costs by earlier introduction of biologics/AIT. This not only includes medical care and drug therapy costs but also the increased economic benefit of helping patients to reduce absenteeism and presenteeism at school or work and in severe cases permit a return to the workplace. Physicians are trained to control disease but the new paradigm is to assess disease remission. Even in cases where remission can only be achieved with continuing treatment, it is still an important goal.[70]

5 | PATIENT ADVOCACY AND ETHICAL CONSIDERATIONS IN RESPIRATORY CARE

It is estimated that one-third of the population suffers from respiratory diseases, with many experiencing symptoms since childhood.[38,39] The number of cases continues to rise and warranting the development of preventive strategies and optimal care. Patients should be involved in designing and agreeing to their own therapeutic plans, and EUFOREA has already addressed this in their developments of Pocket Guides.[14,38,39,68]

Patients often suffer through long disease journeys with limited multidisciplinary collaboration and under-diagnosis.[1] There is limited focus on lifestyle prevention, personalized care, prediction of outcomes, and on patient engagement.[2] We should strive to offer the most appropriate treatment options to the right patients, as this is not only the best approach, but also cost-effective for society and the most ethical choice. In clinical practice, there is a limited stepwise approach to medical care, heterogeneous treatment goals, restricted investment in non-surgical alternatives, and insufficient information given to patients on success prediction and alternative options.[1,2] There is scope for improvement.

Several measures need to be taken to help children with respiratory diseases and other atopic manifestations- good quality of life, normal thriving and avoidance of unnecessary restrictions (diet) have to be key. Firstly, there is a need for experts who can connect these diseases with comorbidities or new associated diseases.[96] Secondly, a comprehensive education program must be provided for general practitioners focusing on prevention. At the medical school level, there is significant scope for enhancing patient advocacy. Students must be able to effectively communicate with patients, tailor their approach to individual needs, use lay terms, and ask appropriate questions. Lastly, coverage and access to treatments should be harmonized and homogenized to ensure equal quality access for all patients. Misdiagnosis of asthma is prevalent in primary care, indicating that guidelines and education for patients and GPs require adaptations. EUFOREA provides solutions such as implementing optimal care, promoting multidisciplinary collaboration, increasing equity in access to care, prioritizing prevention, emphasizing optimal care, and ensuring consistency in care guidelines to combat this epidemic effectively.

Free and regular access to digital tools and good health literacy is crucial for patients to comprehend the physician's advice accurately and understand the implications of their disease and treatments. There is a need to increase health literacy in Europe and join efforts to provide public health education from a young age in order to prevent diseases, recognize symptoms, reduce stigma, and build trust in science and in the healthcare systems. Prevalent issues such as corticophobia can be addressed through appropriate tools so that more objective information is available during the medical consultations.[97] It is also an important factor for healthcare interventions to succeed.

Digital health technologies are powerful tools that may help to overcome barriers to health literacy in order to improve access to healthcare beyond geographic and economic barriers.[98] Several diseases, such as AR, AD and chronic urticaria, now offer the possibility of an initial physical consultation with a doctor combined with regular data collection and patient feedback via apps. This option saves time, provides a more personalized treatment for each patient, and enables feedback to be received. This does not replace patient education on the site or the physician's space, but it can certainly be a useful tool.[99,100]

Fostering doctor–patient communication and partnerships is vital. This addresses trust and the ability in understanding each other's role in advancing health based on respect, mutual sharing, and co-decision. It is essential to avoid imposing treatments on patients and instead, options should be discussed with them. Patients should be and feel involved and joint decisions should be achieved (Table 4).

TABLE 4 Unmet needs in pediatric type 2 inflammation.

Unmet needs in pediatric type 2 inflammation

Need to increase health literacy	Foster physician-patient communication	Personalize disease management and treatment
Joint efforts to provide public health education from a young age, to help prevent disease, recognize symptoms and reduce stigma	Avoid working in silos rather understand each other's role in advancing health, based respect, mutual sharing and co-decision	Treat the person with the disease, not just the disease, as Type 2 diseases are multidimensional and affect life as a whole
Build trust in science and healthcare systems	Encourage patients' groups collaboration with medical societies and vice versa	Provide patient/carer education about treatment options and management styles and accompany patients and carers in excelling the choices that fit them
Improve access to healthcare and reduce inequalities	Invest time on discussing patient's/carer's concerns	Avoid imposing treatments and instead discuss options

6 | CONCLUSION

The EUFOREUM 2023 offered a unique perspective on type 2 inflammatory diseases, with a childhood focus on optimal care, prevention, and remission. This group considers it imperative to invest more in research, education, and advocacy, items that are included in the EUFOREA portfolio of activities for 2024 and beyond. New therapeutic drugs with a systemic approach and a good safety profile offer new opportunities for children with severe manifestations of type 2 disease. This historic opportunity should be seized for the benefit of the patient and should be used to study potential disease-modifying effects and prevention. Collaboration and registry development is essential in this endeavor.

AUTHOR CONTRIBUTIONS

Diego M. Conti: Conceptualization; investigation; methodology; supervision; writing – original draft. **Backer Vibeke:** Conceptualization; investigation; methodology; supervision; writing – review and editing. **Beyer Kirsten:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Bjermer Leif:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Chaker Adam:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Dramburg Stephanie:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Gaga Mina:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Gappa Monika:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Gevaert Philippe:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Hamelmann Eckard:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Peter W. Hellings:** Conceptualization; investigation; methodology; supervision; resources. **Jesenak Milos:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Matthias V. Kopp:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Maurer Marcus:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Podesta Marcia:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Ryan Dermot:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Glenis K. Scadding:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Wüstenberg Eike:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Wahn Ulrich:** Conceptualization; investigation; methodology; writing – review and editing; supervision. **Lau Susanne:** Conceptualization; investigation; methodology; writing – review and editing; supervision; writing – original draft.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

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