NEW CONCEPTS IN PEDIATRIC RHINITIS

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Abstract

Rhinitis and especially allergic rhinitis (AR) remain the most frequent hypersensitivity condition, affecting up to a quarter of the population and impacting upon the quality of life of individual patients and the health economy. Data, especially in respect to underlying pathophysiological mechanisms mainly derive from adult studies and are subsequently extrapolated in the pediatric population. Therapeutic algorithms for children with rhinitis in children are long based on the same principles as in adults. We explore and describe novel aspects of rhinitis, ranging from mechanisms to disease classification, phenotypes, diagnostic and monitoring tools, and the use of treatments, with focus on the traits of pediatric age groups.

Key message

In this review, we describe novel aspects of pediatric rhinitis, from mechanisms to phenotypes, diagnostic and monitoring tools, and the use of treatments, focusing on the traits of pediatric age groups.

Type 2 innate lymphoid cells and defective Treg cells may play a critical role in the pathogenesis of AR. Recent studies have identified the neural pathways and mediators implicated in nasal hyperreactivity in children, after exposure to environmental factors (pollutants, viruses, allergens). Local allergic rhinitis is present and probably underdiagnosed in pediatric populations. Polysensitization to inhalant allergens is associated with multimorbidity of allergy-associated diseases.

Personalized management of allergic rhinitis relies on the proper assessment of disease control, a combination of multiple measurable parameters with patient-reported outcomes, especially when validated for children, being quite valuable. E-Health applications are revolutionizing healthcare services, but data on their impact on pediatric allergic diseases are scarce.

Second-generation antihistamines for mild and intranasal corticosteroids for moderate-to-severe cases are the mainstay of allergic rhinitis treatment in children. Data from real-world studies have confirmed that allergen immunotherapy can prevent the occurrence of asthma in both adults and children with AR. The need for global policies to mitigate pollution and climate change is more relevant than ever.

Introduction

Allergic rhinitis (AR) remains the most frequent hypersensitivity condition, affecting up to a quarter of the population and impacting upon the quality of life of individual patients and the health economy as a whole [1]. The complexity and variability of rhinitis is particularly apparent in childhood, during which anatomical, physiological, immunological and microbiological maturation, generates clinical patterns that are difficult to generalize, but also to manage [2]. Nevertheless, in the last few years, new concepts emerging regarding the

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overall understanding and management of rhinitis are having an influence on the way we see pediatric allergic rhinitis today[3]. In this review, we explore and describe novel aspects of rhinitis, ranging from mechanisms to disease classification, phenotypes, diagnostic and monitoring tools and use of treatments, with particular focus on the traits of pediatric age groups.

Mechanisms

The immunological processes underlying IgE-mediated AR are not dissimilar in children and adults, involving activation of the adaptive immunity and class switching towards production of IgE antibodies. Nevertheless, the vast amount of evidence derives from adult studies with extrapolation on younger ages, while data from mechanistic studies in children are limited. Of importance, despite innate immunity being present from infancy, quantitative differences and qualitative maturation, potentially affecting downstream responses have been observed from early life though preschool and teenage years [4]. AR, which constitutes the most studied phenotype of Pediatric rhinitis, is predominantly defined by type 2 inflammation, mediated by type 2 innate lymphoid cells (ILC2) and Th2 lymphocyte-driven responses locally and systematically[5]. In addition, infiltration of multiple inflammatory cells in the nasal mucosa including T cells, eosinophils, neutrophils, and mast cells has been confirmed [6]. Activated/damaged by aeroallergens nasal epithelial cells secrete matrix metalloproteinase, IL-25, IL-31, IL-33 and thymic stromal lymphopoietin (TSLP), which augment Th2 inflammation either via ILC2s or through antigen presenting cells located underneath the nasal epithelium [7]. ILC2s express receptors such as CRTh2, CD127 (the interleukin 7 receptor) and ST-2, the receptor for IL-33 and release particularly IL-9, IL-5 and IL-13, further activating type 2 inflammation. ILC2s also express high levels of GATA3, contributing to CD4+ Th2 activation and subsequent release of IL-4, IL-5, IL-9 and IL-13, which maintain the Th2-cell lineage and furthermore interact with B lymphocytes to induce class-switching and synthesis of allergen-specific IgE (IgE sensitization) [8]. On re-exposure cross—linking of sIgE on effector cells induce the early, within 2-4 hours and subsequently the late phase response characterized predominant by a sustained nasal congestion [9]. In an ex-vivo model, the presence of ILC2s, myeloid and plasmacytoid dendritic cells (mDCs and pDCs respectively) was documented in the nasal mucosa of AR patients. Of importance, mDCs promoted ILC2 function and proliferation by the IL-33/ST2 pathway, while activation of pDCs suppressed ILC2 function through IL-6 in AR patients, suggesting a differential role for distinct dendritic cell subtypes [10].

T regulatory cells (Tregs) are key mediators in immune regulation thus prevent airway allergic inflammation. Inflammation in AR appears to be a functional defect of Tregs which results in decreased production of IL-10 and transforming growth factor (TGF)-β [11]. Certain microRNAs (miRNAs) mediate Treg function [12]. In children with AR, miR-155 promoted Treg differentiation in CD4+ T cells, while other miRNA mediate response to respiratory infections, providing new potential treatment targets [13]. Moreover, other less studied T cell populations, such as the gammadelta (γ δ) T cells, that facilitate eosinophil migration, were significantly more abundant in the nasal mucosa of AR patients compared to controls, while their number and distribution were positively associated with eosinophils, macrophages and mast cells locally, suggesting an essential role in mucosal inflammation [14]. Earlier studies showed a dysregulated pattern of Th1 transcription factors such as STAT6+ and GATA3+ potentially contributing to the enhance Th2 responses in AR patients compared to controls [15]. More recently the Notch signaling pathway which downregulates FOXp3 expression and differentiation of T-reg was significantly elevated in AR patients [16].

Studies on the role of B-cells in the pathogenesis of AR, indicate a significant skewing of circulating B-cell population towards memory B cells with markedly increased expression of CD23, which facilitate antigen presentation and IgE synthesis in AR patients [17]; nevertheless, other studies were not confirmatory of differences in B-regulatory cell populations or Il-10 production [18].

Recently, AR patients were shown to exhibit increased number of specific sets of activated neutrophils -CD16(high)-CD62L(dim) either locally or systematically, resulting in T cell priming and enhancing eosinophil migration [19]. Recently, activated neutrophils were shown to serve as functional antigen presenting cells (APC) in late phase reactions and activate allergen-specific effector CD4+ T-cells to synthesize cytokines, thus they potentially contribute to magnified nasal allergic inflammation [20].

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There is evidence that autophagy, a catabolic intracellular process playing a substantial role in maintaining tissue and cellular homeostasis, is implicated in immune response regulation and asthma pathogenesis [21]. More recently, highly expressed autophagic markers were observed in the upper airways of AR patients, strongly associated with indices of nasal remodeling [22].

Phenotypes and endotypes

The concepts of phenotype and endotype have been increasingly used to characterize variants under a wider disease umbrella, referring to either the apparent differentiating features (phenotype) or the underlying mechanisms (endotype). While disease variability is clearly the norm rather than the exception in regards to most allergic diseases, the realization that treatment response may vary radially between groups, has given impetus to this approach [23]. Unfortunately, lack of pathognomonic biomarkers, considerable overlap and unstable temporal dynamics have not allowed, for the time being, the construction of conclusive phenotype and/or endotype-based guidelines [24]. Nevertheless, clear distinctions and differentiating factors can be drawn, such as the hormonal or gustatory rhinitis – all part of the non-allergic rhinitis spectrum. A distinct pediatric example is rhinitis in infants, which presents additional challenges in management choices, requiring further evidence [25].

Non allergic rhinitis (NAR)

Non allergic rhinitis in children is poorly defined [26]. Previously AR was clearly discriminated by NAR by means of increased local total/local IgE specific levels and nasal eosinophils and these differences were more pronounced in children than adults with AR, suggesting that AR in children is a more distinct feature [27]. However, inflammatory mediators related to different inflammatory endotypes detected from nasal cytology cannot discriminate AR from NAR adult patients [28].

Local allergic rhinitis (LAR) in children is an emerging disease, highly underdiagnosed [29]. Increased levels of local IgE in the nasal lavage fluid has been proposed as a useful biomarker in children with suspected LAR [30]. Local production of "T2" inflammatory mediators has been demonstrated following nasal allergen challenges in a pediatric setting [31]. Nevertheless, AR and LAR share several clinical and immune features, such as positive response to a nasal allergen provocation test, increased risk of asthma occurrence and increased nasal IgE production [32]. Moreover, the FcepsilonR1beta genetic polymorphism has been linked both with LAR and AR prevalence [33].

Nasal hyperreactivity (NHR) constitutes a cardinal clinical feature both in AR and NAR [34] and has been previously documented in children with allergic rhinitis, although respective techniques are difficult to apply in clinical use and young ages [35, 36]. The most well described pathogenetic mechanism involves a "dysregulated" neural innervation network. In NAR and NHR, the role of the efferent component via the activated transient receptor potential (TRP) ion channels (receptor 1_TRPA1 and subfamily V-TRPV1), induces the release of neuropeptides, such as CGRP and substance P (SP), neurokinin A and B from sensory nerve endings, which in turn induce sneezing, mucus production and congestion [37]. In line, histological data are indicative of increased expression of the aforementioned neuropeptides of the nasal mucosa in patients with NHR and NAR [38]. Moreover, the impact of environmental and microbial factors (i.e.; staphylococcus Aureus enterotoxins) has been postulated for triggering local nerve endings, more so in the presence of a disrupted epithelium barrier [39]. It remains to be elucidated whether barrier dysfunction is a primary (genetic) defect or secondary to infectious agents or allergens [40, 41].

Multimorbidity

The term multimorbidity is used to indicate the clustering and co-occurrence of different diseases in an individual, where, conceptually, a "primary" disease in not obvious [42]. Epidemiological data suggest that rhinitis/rhinoconjunctivitis, asthma and dermatitis form a multimorbidity cluster, attributed to shared genetic polymorphisms and pathogenetic mechanisms [43]. The MeDALL (Mechanisms of the Development of ALLergy) project, including more than 12.000 children from 12 ongoing longitudinal cohort studies, clearly showed that co-existence of asthma, rhinitis and eczema in the same child is more prevalent than

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expected by chance [44]. IgE (poly) sensitization was acknowledged as a fundamental component of a specific phenotypical presentation, although not the sole one, significantly associated with disease severity and multimorbidity risk [45]. Moreover, prospective studies indicate that either sensitization per se, or early polysensitization and co-sensitization to both perennial and seasonal allergens, or to furry animals and molds, in case of sole perennial sensitization, are associated with enhanced likelihood of AR patients to present other allergy-associated diseases [46, 47]; however, it is well accepted that a significant proportion of children with IgE sensitization do not develop any allergy-associated disease [48]. In line, molecular studies identified eosinophilic-mediated pathways, including IL-4 and GATA3-related signals, with their respective induced proteins as prominent mediators in allergic multimorbidity [49]; nevertheless, more recently other cell types and pathways have also been implicated in the AR-multimorbidity such as TLR and IL-1 mediated responses [50]. In respect to the implicated genes, several independent risk variants are identified with allergic diseases specific effects have been identified, potentially by dysregulating the expression of lymphocyte-mediated immunity [51]. A recent meta-analysis of worldwide asthma-genome associations studies, verified two loci (8q21.13 and 16p13.13) implicated in the comorbidity of asthma and AR [52].

In respect to allergy-associated disease progression, the MAS study showed that parental history of allergy and broad polymolecular IgE sensitization is a risk factor for presenting allergic multimorbidity later in life [53]. From another perspective, AR combined with ocular and skin allergic diseases is strongly associated with asthma occurrence in adulthood, although this association wanes with age [54]. Sex and puberty-related mechanisms are thought to be related in the "sex shift" prevalence, from male to female predominance after puberty, of allergic multimorbidity, as shown from individual participant data (IPD) meta-analyses in the MeDALL and other cohorts [55]. Of importance, patients with allergic multimorbidity present increased disease burden, drug and healthcare use and costs in all age groups [56].

Control

In accordance to the WHO proposal for chronic allergic diseases and in parallel to the GINA guidelines for asthma, the concept of control was introduced in AR, as a more feasible measure of both severity and response to treatment [57, 58]. Most recent AR management algorithms propose a stepwise approach based on the level of control achieved by a therapeutic intervention [23, 59]. A series of criteria to evaluate control were proposed in the PRACTAL report, including assessing symptom severity, quality of life (QoL) by means of disease burden at school, leisure and sleep, and upper respiratory function by objective measurements such as nasal flow and/or patency. Information regarding rescue medication use and (uncontrolled) comorbidities such as sinusitis and/or asthma are also considered relevant [23].

Patient reported outcome measures (PROMs) are currently acknowledged as valuable tools for assessing disease morbidity in a standard clinical setting. In respect to AR patients the Allergic Rhinitis Control Test (ARCT) [60] and the Pediatric Control of Allergic Rhinitis and Asthma test (CARATkids) [61, 62] have been validated for children and adolescents while the Rhinitis Control Assessment Test (RCAT) is currently validated only for adolescents [63]. The Visual Analogue Scale (VAS) is validated for control assessment only in adults with AR, however it can be used in all ages including preschool children by proxy [64, 65]. Thus, the ARIA algorithm has implemented VAS measurements for daily monitoring in a mobile app for patients over 12 years of age [66]. Nevertheless, it is well known that PROMs can be influenced by poor adherence to treatment, patient's perceptions regarding disease' severity and the individual's psychosocial background [58].

eHealth and mHealth

eHealth refers to the application of information and communication technologies (ICT) in healthcare services. The WHO acknowledges digital technology potential and encourages health systems to endorse, improve and prioritize its implementation to benefit in terms of accessibility, quality, and affordability of health care [67]. The term "mobile health" (mHealth) refers to the use of mobile, wireless technologies to health practice and research in this respect [68].

Smartphones are most promising in promoting and supporting public health, as they are widely available,

equipped with sophisticated microprocessors and a range of sensors which can communicate with other mobile devices, and provide access to the internet even in remote locations. As of mid-2020, 3.5 billion smartphones are in use, by approximately 41% of the world's population [69]. In the USA, 95% of teens have access to a smartphone and 83% use it for learning purposes [70].

AR is often regarded as trivial by both patients and physicians and thus not always managed properly. mHealth applications (apps) aim at implementing personalized medicine strategies to patients and caregivers by monitoring symptoms, visualizing the burden of the disease, thus improving health literacy, and ultimately engaging in self-management and shared decision making [71]. Moreover, eHealth services can override access barriers to healthcare and reduce costs while providing healthcare professionals with real-life data on several aspects of the disease and its impact that otherwise would be difficult to identify.

Adherence to treatment is a common problem in chronic respiratory diseases, such as AR, moreover in adolescents [72]. In the MASK study, where a mobile app was used to assess real-world data from adolescents and adults with AR, non-adherence was observed in 69% of participants. The effect of e-health services on adherence to nasal steroids was studied in a randomized trial including children 5-18 years old with moderate-severe seasonal AR [73]. Patients that used an internet-based telemonitoring system instead of hard copy diaries, were significantly more adherent to treatment and better educated on their disease, although symptom scores and QoL were not affected. In addition, services such as updates on local pollen counts, online medical access and SMS reminders in case of missed entries can be provided.

mHealth apps are a booming market and caution should be taken on their credibility. Up to day, only a few apps on AR have been validated, while safety and efficacy data are scarce [74]. A recent study showed that the majority of mobile apps providing grass pollen forecasts are inaccurate and potentially harmful [75]. mHealth apps are now acknowledged as medical devices by both the EU and FDA [76], although FDA reserves the concern of potentially applying regulations in case of identifying risk on patient's safety [77]. In Europe, the General Data Protection Regulation is also applied to manufacturers for ensuring consumers' data privacy [78]. A stricter framework of regulations should be expected soon.

Currently, only a few mobile apps that monitor symptoms of both AR and asthma are available [74, 79]. Mask-air and Allergy Monitor allow patients to assess the time course of symptoms relative to treatment and the effect of AR on sleep, productivity, QoL, etc. by sharing information digitally [80]. Additionally, notifications prompt answering clinical questionnaires and treatment adherence daily [81]. In case of symptom worsening, patients are alerted to step up treatment or contact their doctor for consultation. These are key features for encouraging self-awareness and self-empowerment, especially in chronic diseases like AR, where patients or their caregivers are responsible for treatment administration [82]. Mask-air, a validated tool for assessing AR control in adolescents and adults, may also be integrated into a Clinical Decision Support System that guides clinicians into pertinent interventions depending on their patient's status [83]. Evolving algorithms are currently exploring the possibility of data input automation, to improve uptake [84].

Treatment/medications

Therapeutic algorithms for children with rhinitis in children are long based on the same principles as in adults [85]. During the past two decades ARIA has proposed an evolving guideline for the management of patients with AR. More recently, intergraded care pathways (ICPs) have been proposed, based on technology-evident information, providing a self-care plan by a multidisciplinary group of health professionals centered around the patient [59]. In specific, an algorithm based on the visual analogue scale (VAS) for assessing rhinitis symptoms has been revised by the ARIA expert group for (1) selection of pharmacotherapy for patients with AR and (2) to tailor treatment depending on control [86].

ARIA has been the first guideline in the field of allergy to have used the GRADE system to formally evaluate and appraise evidence. In its latest update, an important step is the addition or real-life evidence, supported through an mHealth application [59]. Real-life approaches are increasingly used to complement randomized trials, in order to expand the scope and evaluate external validity of the findings [87].

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Treatment of AR includes allergen avoidance whenever possible, use of medications and allergen specific immunotherapy (AIT)

Environmental interventions

Certain interventions aiming at reduced allergen (pollen, molds, house dust mites, pets) or irritant (pollutants, tobacco smoke) exposure have long been incorporated into the guidelines [57]. There is substantial evidence that sensitization/exposure to molds correlates significantly with exacerbation of AR symptoms, even in children with non-allergic rhinitis [29, 88]. Mold and cockroach allergen reduction leading to subsequent symptom relief, can be achieved by combined interventions [89]. In general, control of indoor allergen exposure in allergic subjects, is effective when multifaceted and demanding approaches are followed [90]. With regards to house dust mite control, although previous meta-analyses showed minimal protective effects of interventions aiming at exposure reduction, recent data deriving from asthmatic patients indicate that certain actions, such as mite-impermeable bed encasings, may confer significant protection form disease morbidity [91]. It is plausible that early, prolonged and personalized interventions, tailored to individual sensitization and exposure status, can be clinically beneficial [92].

Exposure to AR-relevant outdoor pollens and molds can be reduced by limiting exposure and field activities during peak pollen days, however such recommendation is often unrealistic in the pediatric population and counters the goal of reinforcing daily activity in children [93].

Various epidemiological studies have shown that exposure to volatile organic compounds

from building materials and consumer products exacerbate rhinitis symptoms and although data on the effects on rhinitis of air pollution exposure per se are inconsistent [94, 95], their capacity to increase the allergenicity and immunogenicity of aeroallergens has been shown [96]. Heightened CO_2 levels and global climate change have been strongly associated with increased prevalence of rhinitis symptoms, by increase in pollen levels both in volume and in time; policy adjustments have recently been addressed in order to decrease pollution and mitigate their effects on allergy-associated diseases [97]

Pharmacotherapy

Medications used for the treatment of AR in children include non-sedating H1-antihistamines, leukotriene receptor antagonists, chromones, intranasal corticosteroids (INCSs) and combination of INCs and azelastine.

Antihistamines

Antihistamines are available as oral, intranasal, and ocular preparations. Oral first generation, sedating antihistamines are no longer recommended for the treatment of pediatric rhinitis due to their impaired safety profile often associated with cardiac arrhythmias, drowsiness, confusion, vision, and mental disorders etc. Of importance, a recent report using data from the World Health Organization (WHO) database, showed that the use of certain antihistamines has been strongly associated with severe and unexpected reactions, more so in preschoolers, where off-label use is frequent [98]. Second generation antihistamines present a significantly improved safety profile due to their high H1-receptor selectivity, low brain permeability and longer duration of action [99]. Recently, cardiac rhythm safety was documented for certain 2nd generation antihistamines, such as bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, mizolastine and rupatadine, even in the case of quadrupling the recommended standard dose [100]. Antihistamines, act predominantly on neutrally mediated symptoms such as sneeze, rhinorrhea, and nasal itch. They should be used continuously, rather than no-demand in persistent rhinitis patients [93]. Topical/nasal antihistamines have rapid onset of action and minimum side effects [101]. In addition, azelastine has been shown to have mast cell-stabilizing, anti-leukotriene, anti-inflammatory and immunomodulatory effects [102].

Intranasal corticosteroids (INCs)

INSc are the mainstay, particularly for moderate-to-severe allergic rhinitis, due to their anti-inflammatory properties and significant attenuation of late phase allergic reaction, thus acting on nasal congestion [59, 103]. In respect to non-allergic rhinitis, a recent Cochrane review showed that INCs use has only short term

beneficial effects on symptom severity, potentially depending on individual phenotypic characteristics [104]. INCs have a rapid onset of action, while the newer preparations such as mometasone furoate, fluticasone furoate (FP) and fluticasone propionate present negligible systemic absorption, thus they are mostly suitable for children [105]. On-demand use can be an efficacious alternative in children with seasonal AR symptoms, especially in families with safety concerns on daily CS use, in order to increase adherence [106]. Recently, an ARIA-EAACI statement suggested that, based on current evidence, patients with COVID-19 infection should not discontinue their INCS prescribed for AR symptoms [107].

The recently formulated combination of azelastine and fluticasone propionate (FP) has shown short and long term efficacy, with superiority over FP both in speed of action and symptom relief, in children with AR [108, 109]. Safety and tolerability have been documented in children over 4-years of age, with minimal local adverse reactions such as dysgeusia [110]. The combination has been granted approval for use in children over 6 years of age by the U.S. Food and Drug Administration [111].

Antagonists of leukotriene receptors (LTRA) block cysteinyl leukotrienes receptors, which are important mediators of the inflammatory response in both AR and asthma [112]. Several studies have shown inferiority of LTRA compared to INCS and SGHA as therapeutic choices in AR, while as of 03/04/2020 FDA required a boxed warning, based on limited data reporting serious mental health side effects, thus restricting montelukast use for AR [113].

Biologicals

Uncontrolled and severe forms of AR with substantial impact on quality of life, have been considered as a potential target for biologicals [114]. Recent reports and meta-analysis showed that anti-IgE (omalizumab) significantly reduces rhinitis morbidity, severity and rescue medication use and improve quality of life in uncontrolled adolescents [115, 116]. There are also data indicating that pre-treatment with anti-IgE in children undergoing seasonal AIT, significantly decrease severe adverse reactions and improves daily rhinitis symptoms [117]; nevertheless, Omalizumab is not indicated in AR due to cost limitation.

Dupilumab is an anti-IL-4 monoclonal antibody currently approved for uncontrolled atopic dermatitis and asthma [118]. In a Phase IIb clinical trial dupilumab was efficient in ameliorating rhinitis symptoms such as postnasal discharge, nasal blockage, runny nose and sneezing, in patients with uncontrolled asthma and perennial AR [119]. The results from a clinical study evaluating the efficacy of dupilumab as an adjuvant therapy in patients undergoing AIT are awaited[120].

Alternative therapies

Nasal saline irrigation has long been perceived as an adjunct treatment for rhinitis, although efficacy was only recently documented in a meta-analysis with no reported adverse reactions [121]. Recently, a real life study in children showed significant improvement of AR symptoms and reduction of medications, as these were assessed by VAS and CARAT, when nasal irrigation was added to standard treatment [122].

Use of nasal filters in AR adults with grass allergy during a natural in season exposure, provided significant efficacy, by means of improved nasal symptom score, while safety and usability were also documented [123]. It is however uncertain whether such intervention may be tolerable in children. In respect to other 'alternative' treatments, acupuncture has moderate to high evidence of efficacy for the treatment of subjects with rhinitis, while butterbar has shown showed moderate beneficial effects on AR symptoms [124]. Capsaicin is efficient for the treatment of non-AR in adults; however pediatric studies are lacking [125].

Immunotherapy

Allergen immunotherapy (AIT), either in the subcutaneous (SCIT) or sublingual (SLIT) form, has long been shown to result in improved AR control in all age groups and aspires to be the only etiologic treatment for respiratory allergies (allergic rhinitis (AR) and asthma) through induction of immunologic tolerance [126] [127]. Pooled analyses support the complementary use of AIT on pharmacotherapy in AR patients moreover due to achievement of long-lasting therapeutic effect [128]. Recently, data from a real-world study confirmed

the medication sparing effect and long-term symptom relief following AIT, in a cohort of grass AR patients, including children. In agreement, subcutaneous allergoid immunotherapy in house dust mite AR children resulted in significant reduction in AR and asthma medication, even after long-term cessation of AIT [129].

Early-onset asthma is largely associated with IgE sensitization and AR [130], thus AIT has long been suggested as a disease modifying strategy potentially preventing allergen sensitization and asthma occurrence in children with AR [131]. Although early clinical studies showed a preventive effect of AIT on the occurrence of new sensitizations in children with rhinitis [132], this is still inconclusive [133]. A recent meta-analysis identified a short term preventive effect of AIT on novel sensitization development; nevertheless, the included studies were highly heterogenous [134]. Nevertheless, the preventive effects of AIT on asthma development and progression has been confirmed in real-world studies, assessing the effect of SLIT immunotherapy in grass pollen subjects with AR [135]. Moreover, a long-term randomized controlled trial, the Grazax Asthma Prevention (GAP) study, [136], showed significantly lower and long-lasting incidence of asthma following 3-year AIT in grass AR subjects, while significant lower levels of total and allergen specific IgE and reductions in skin prick test response to grass were noted [137].

Conclusion

While the amount of knowledge on rhinitis and allergic rhinitis in children is continuously increasing, novel approaches mostly deriving from adult populations, have the potential of improving outcomes in children. Considering that blinded randomized trials are more difficult to perform in pediatrics, real-life approaches may be used to confirm the usefulness of these proposals[138]. It is probable that, as in the case of pediatric asthma [139], prevention studies and interventions on the natural history of rhinitis and/or respiratory allergy as a whole, are the highest priority for research and health policy.

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