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Latest developments in Allergic Rhinitis in *Allergy* for Clinicians and Researchers

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ABSTRACT

Research efforts in allergic rhinitis has always been intense. Over the past 3 years, numerous breakthroughs in basic science and clinical research have been made, augmenting our understanding of this condition that afflicts a significant proportion of the global population. New epidemiological findings, novel insights into the molecular and cellular mechanisms of allergy, enhancement of current developmental theories, new concepts of the goals and endpoints of management, latest therapeutic modalities that includes the harnessing of information technology and big data are some areas where important advances were made. We attempt to bring you a summary of the key research advances made in the field of allergic rhinitis from 2013 to 2015.

INTRODUCTION

Allergic rhinitis (AR) is a common condition that affects a significant proportion of the global population, across all age groups and is often a life-long condition. Its impact on direct and indirect healthcare costs are significant and it negatively impacts patients' quality of life, work performance and social functioning(1). Overall, AR poses a significant public health burden. Research efforts on AR had been intensive given its significance. Busy clinicians and scientists might find it difficult to keep up with the plethora of published articles and sift out the salient points. We performed this review of articles published mainly in **Allergy** (2013-2015), a representative journal in the field, to provide an update on important research findings on AR.

Interesting research findings on the epidemiology, developmental theories and pathophysiology, novel technology and management, have emerged. However, these studies are of diverse and unique content. We grouped these studies into a coherent bundle, which might aid in contextual understanding and interpretation. Areas of debate and uncertainty are discussed for potential research to be considered for the clarification of these knowledge gaps.

PREVALENCE, BURDEN AND COMORBIDITIES OF AR

1. Pre-school children: A neglected population

The international ISAAC studies have elucidated the prevalence of AR, AD and asthma in children above the age of 6 and have enhanced our understanding of allergy in paediatric populations(2, 3). Data in preschool children is, however, lacking. A nation-wide study in Portugal found that 43.4% of preschool children had rhinitis based on an adapted ISAAC questionnaire(4). A Brazilian study used Phase III EISL and modified ISAAC questionnaires to assess rhinitis symptoms in infants aged 12 to 15 months. This study found that 48.3% of children had at least one sneezing, runny or blocked nose without cold or flu in the first year of life, and a quarter of infants had recurrent wheezing (≥ 3 episodes) and wheezing was more frequent in the presence of AR symptoms(5). A higher prevalence in preschool children may be expected as infectious rhinitis or other types of rhinitis is common due to a wide spectrum of risk factors (e.g., viruses, bacteria, molds and other stimuli), and the immaturity of the immune system(6). Longitudinal studies are needed in this group of children.

2. The costs of AR

As a Global Allergy and Asthma European Network (GA²LEN) initiative, Zuberbier et al. conducted a detailed cost analysis of allergy treatment in the European Union (EU) and found that the cost of insufficiently-treated patients range between €55 and €151 billion annually from absenteeism and productivity losses(7). This translates to €2405 per untreated patient annually. The cost of treatment is €125 per patient annually, or only 5% of the costs of non-treatment. Adequately treating allergic patients is cost-effective, rendering potential savings of up to €142 billion per annum for the EU. With increasing prevalence of allergic diseases, the current specialist-based model of care for allergy may increasingly be inadequate in meeting the disease burden and entails high costs. In a Position paper by Jutel et al(8), a holistic primary care model for management of allergic diseases was proposed to decant the load off tertiary centres and improve patient access to allergy-centric care in the primary care setting. The costs of management of allergic diseases is likely lower in primary care compared to tertiary centres. However, treatment outcomes and actual cost savings require detailed analysis.

3. Impact on daily function

It is known that AR impacts daily function. AR patients subjected to nasal provocation exhibited impaired driving performance comparable to blood alcohol level of 0.05%, the legal limit in some countries. Treatment with intranasal steroids and antihistamine partially alleviated the impairment(9). Su et al. found in a cohort of 128118 males (64059 AR patients vs 64059 matched controls), the hazard ratio for erectile dysfunction (ED) was 1.37 (95% CI, 1.24–1.52; $p < 0.001$) in those with AR(10). AR may be a potential risk factor for ED, and the risk probably increases with AR severity.

4. AR and asthma

In a population-based study, children participating in a cohort study (n=906) were reviewed at age of 8 years. The results showed that the OR of asthmatics with AR experiencing frequent wheezing was 2.89 (95% CI 1.41–5.91) and 3.44 (95% CI 1.19–9.94) for severe wheezing attacks limiting speech(11). In another study, after moderate to severe asthma exacerbation, children with AR had higher odds of delayed (>7 days) recovery of pulmonary function tests (PFT) (OR 4.3, 95% CI 1.29–14.67)(12). These findings lend support to the unified airway theory and inform clinicians of the need to consider and manage AR in asthmatics and *vice versa*. A meta-analysis found that intranasal corticosteroid medications significantly improve some asthma-specific outcome measures in patients suffering from both AR and asthma(13). It will be interesting to determine the role of nasal inhalation technique as monotherapy in patients suffering from both asthma and AR in future studies(13).

5. AR and chronic rhinosinusitis

AR and chronic rhinosinusitis (CRS) are frequently seen together. An common question is whether AR leads to CRS. Georgalas et al performed a review on existing literature based on a modified Bradford-Hill criteria for causality between AR and CRS in adults and children(14). They found that existing studies on the topic are heterogeneous in methods and quality. There is inadequate evidence for a causal relationship.

RISK FACTORS FOR AR AND ALLERGEN SENSITIZATION (Figure 1)

1. Population genetic studies

Though the genetic basis of AR has been evaluated intensively, the entire hereditary profile of AR has yet to be fully clarified because allergic diseases result from a complex interplay between genes and the environment as well as the age at which the exposure occurs (e.g., for *GSTP1* gene(15)). Future studies need to have larger samples sizes to detect the effect of gene-gene interactions and the role of the environment in the expression of disease.

In a longitudinal cohort study, allele frequencies of 39 single nucleotide polymorphisms (SNPs) were investigated for association with the exact allergic phenotypes of three genomewide metastudies in Sweden. Among them, 12 SNPs were found to be associated with AR. The *TLR6-TLR1* locus likely has a central role in the development of allergic disease. The associations between genetic variation in the *SSTR1-MIPOL1* and *TSLP-SLC25A46* loci and age at onset is the first report of age-at-onset effects in AR(16). Another study found significant associations between five SNPs in the 17q21 asthma susceptibility locus, rs9303277, rs7216389, rs7224129, rs3744246, and rs4794820, and AR in Japan(17).

Two Japanese population studies demonstrated that *FLG* mutations (an important predisposing factor for atopic dermatitis) are a significant predisposing factor for hay fever with an OR of 2.01 (95% CI 1.027–3.936, $p < 0.05$)(18); and variants (rs9303277, rs7216389, rs7224129, rs3744246, and rs4794820) in the 17q21 asthma susceptibility locus are also associated with AR(17). In addition, the expression of the mRNA of the ORMDL3 gene on this locus was significantly elevated in nasal epithelium(17).

Many other genetic variations, DNA methylation, or changes in miRNA expression profiles have been reported in association with atopy(19-25), asthma(25-30), and atopic dermatitis(31, 32), which are not yet replicated in AR.

2. Variations in allergen sensitization between geographically distinct areas

The large global variation in allergen sensitization patterns suggests that the environment is a critical determinant in sensitization. Studies on migration provide a litmus test for this theory as allergic manifestations should change as patients move between geographically distinct areas.

Casas et al. observed geographical variation in the concentrations of house dust mites (HDM) allergens in house dust, with lower levels in colder and dryer areas and higher in warmer and humid area in Europe(33, 34). Toppila-Salmi et al. confirmed that HDM-sensitization in Finnish asthmatic population was significantly lower (less than 10% in both asthmatics and healthy controls), where poly-sensitization was more prevalent than monosensitization(35). This raises the question on whether HDM-sensitization will increase in people who migrate from Northern to the tropical continents.

Andiappan et al. demonstrated that 70-80 % of Singapore- or Malaysia-born Chinese and less than 20% of recent migrants from China are sensitized to HDM(36). Mono-sensitization to HDM (over 80%) is a typical phenotype in Singapore- or Malaysia-born Chinese as less than 30% of them also had sIgE for other allergens and few of the HDM-sIgE-negative individuals reacted to other allergens. Interestingly, migrants to Singapore, a tropical urban city, increasingly became sensitized to HDM and increasingly demonstrated symptoms of AR and asthma. More than 40% of migrants from China who resided for more than 8 years in Singapore had positive SPT to HDM while less than 20% of those who resided for less than 3 years were sensitized(36).

Gas, dust, and fumes, exposed occupationally, may act as adjuvants that facilitate sensitization to mites and mite-sensitized individuals may especially be susceptible to effects of noxious inhalants(37). Post et al. showed that Ca^{2+} signaling plays a crucial role in barrier dysfunction and the pro-inflammatory response of bronchial epithelium upon HDM exposure and may thus have important implications for the development of allergic asthma(38). Pollen-derived adenosine, a

mediator in ragweed pollen, was found to be a critical cofactor in ragweed-pollen induced allergic airway inflammation(39).

3. Controversies in “atopic march”

The common allergic diseases manifestations are eczema, AR/rhinoconjunctivitis and asthma. They tend to appear in a temporal sequence known as the “atopic march”, which classically begins with eczema in early childhood followed by the appearance of asthma and AR later on(40). This leads to the question of whether eczema is a causative factor in the development of subsequent atopic diseases, or whether these clinical conditions are manifestations of the altered IgE response as the immune system matures.

An analysis of the MeDALL (Mechanisms of the Development of ALLergy) study, involving 17209 children aged 4 years and 14585 children aged 8 years from seven European birth cohorts, statistically partitioned the children into clusters and analyzed at both age periods (41). Two groups were identified in which eczema, AR and asthma had significantly higher prevalence in Group 2 as compared to Group 1 (at 8 years: 27.5%, 49.0% and 36.9% versus 8.0%, 1.8% and 1.1%). After stratification by IgE sensitization, the prevalences were maintained. This study provided statistical evidence that the classic atopic trios are indeed a cluster of allergic comorbidities.

However, the clustering of the atopic trio does not provide the answer to the question of whether one step of the “march” is a causative factor for the next step. The causal theory is an attractive one, as it implies that halting the first step of the “march” may arrest progression to subsequent steps. Proving a hypothesis of causality, especially one as complex as this, requires several approaches, including epidemiological evidence, molecular and physiological evidence, and interventional studies that demonstrate arrest of progression.

Dharmage et al. conducted a review of 17 longitudinal studies(40). These studies are concordant in demonstrating that patients affected by eczema in infancy have higher odds of developing AR and asthma subsequently, providing strong statistical evidence proving the temporal relationship of the atopic march, but it does not constitute proof of causality. The prevailing hypothesis of the causality of eczema to subsequent steps centres around the defective skin barrier leading to penetration by and early sensitization to allergens, initiating the march (**Figure 1**, skin barrier hypothesis). We look forward to upcoming studies on this exciting topic.

4. Parental risk factors

Westman et al. found from birth cohort of 2413 children that isolated parental AR increased the odds of AR (OR 2.2, 95% CI 1.6–3.2), whereas isolated parental asthma or eczema did not(42). Having all 3 atopic conditions (AR, eczema, and asthma) conferred the highest odds for offspring AR (OR 5.6, 95% CI 3.8–8.4) and non-allergic rhinitis (NAR) (OR 4.9, 95% CI 2.8–8.4). The highest prevalence of AR (37.5%) exists in children whose parents had both AR and NAR. Paternal and maternal atopy conferred similar odds of atopy in offsprings. Fuertes et al. found from two large German birth cohort studies that even if the parents developed these atopic conditions after the birth of the child, there is also a positive association with the child developing atopic conditions particularly for asthma (and less consistently so for AR and eczema), and the effect of the association is similar to parents with pre-birth atopy(43).

Andersson et al. reviewed 16 studies (25 analyses) investigating prenatal maternal stress and found that 21 analyses demonstrated positive associations between prenatal maternal stress and atopy(44). Of the 4 analyses dealing with AR, 3 found positive associations with adjusted OR (AOR) ranging between 0.96 and 2.38. Maternal smoking and absence of breastfeeding were found to be stronger predictors of NAR, whereas current wheeze and eczema were stronger predictors of AR(11). Interestingly, HDM (*Der p* 1) allergen was found in human milk and primes for allergic sensitization in a mouse model of asthma(45). This study is a prelude to future studies to identify and determine if factors in breast milk contribute to allergic sensitization(45).

5. Other risk factors for AR and atopic manifestations

Mai et al. found that serum 25(OH)D level <50 nM was associated with increased incidence of AR in men (AOR 2.55, 95% CI 1.01–6.49) with each 25 nM reduction in 25(OH)D level being associated with an AOR of 1.84 (95% CI 1.18–2.87)(46). Interestingly, the association was opposite in women, with an AOR of 0.83 (95% CI 0.66–1.05) for each 25 nM reduction in 25(OH)D level. Low vitamin D serum level is inversely associated with eczema in children and adolescents in Germany(47). These data could support the theory of Vitamin D having immunomodulatory properties, which was also reported in mice(48). A systematic review found that vitamin D supplementation might be effective for preventing asthma exacerbations, but the findings need to be confirmed by clinical trials due to significant heterogeneity amongst studies(49, 50). Neonatal vitamin A supplementation was found to be associated with increased risk of atopy and wheezing(51, 52), especially in girls(51). In a European multicentre birth cohort study, serum vitamin E concentration at 1 year of age was not associated with allergies or asthma at 6 years(53).

The biodiversity hypothesis postulates that decreased exposure of children to environmental microbiota due to loss of green spaces and improved hygiene impacted commensal biodiversity and its effect on immune tolerance. Ruokolainen et al. studied the relationships between amount of green spaces (forested and agricultural areas) around children who were study subjects in 3 Finnish and Estonian studies, and atopy(54). They found that green area within 2–5 km from the home was

inversely and significantly associated with atopic sensitization in children 6 years of age and older. This may demonstrate the environmental effect on commensal microbiota, which has also been shown in atopic eczema(55). Farm exposure and time trends in early childhood were found to influence DNA methylation in genes related to asthma and allergy(56). Farming in Poland has shown a protective effect against objective measures of atopy potentially related to contact with grain or associated farm activities(57). Furthermore, Sozanska et al. showed that the protective effects of larger family size and birth order on atopy were much stronger in children than in adults and among those living in a village(58).

Hahm et al. extracted data from the ISAAC study in South Korea and found that staying in a newly-built home in infancy is associated with higher odds of developing AR at 7-8 years of age (OR 3.09, 95% CI 1.71–5.57)(59). They postulated this could be due to higher concentrations of chemicals, including volatile organic chemicals, in new buildings. Dampness and mould at home were also associated with AR (OR 1.31, 95% CI 1.07–1.61). In addition, exposure to traffic-related air pollution, especially PM_{2.5}, was found to be associated with eczema and hay fever(60). Exposure to antimicrobial chemical, triclosan, in personal care products, was associated with allergic disease in Norway(61). Cigarette smoking was associated with a high prevalence of chronic rhinitis in both sexes but low prevalence of AR in men. (62). Rhinitis was associated with peripheral arterial disease, a predictor of future cerebrovascular and cardiovascular events, independent of the presence of atopy(63).

CELLULAR AND MOLECULAR MECHANISMS OF AR

More evidence showed that allergen exposure locally produces systemic changes at the cellular and molecular levels. Wong et al. investigated circulating peripheral blood mononuclear cells in patients allergic to Bahia grass pollen and controls, and found a small population of circulating allergen-specific B cells that responded quickly when exposed to the specific allergen and proliferated rapidly(64). The behavior of this population of peripheral blood B cells is similar to those of adaptive memory B cells in response to specific allergens, and could be precursors for allergen-specific IgE production and could be one component of the rapid systemic response to allergens(64). In another study, pollen-derived non-allergenic substances (e.g., phytoprostane E1) were found to be responsible for B-cell-dependent aggravation of IgE-mediated allergies(65).

Pilette et al. evaluated dendritic cells (DC) in the nasal mucosa and the skin after nasal allergen challenge (NAC)(66). They found that in AR, DC exhibited aberrant functions both in local tissues and systemically. Both myeloid DC and plasmacytoid DC increased in the nose and skin after NAC. A decrease in IL-10 and IFN- γ were found in the nose, skin and peripheral blood and a decrease in IL-12 was noted in blood. The significance of these findings are that impaired IL-10, IL-12 and IFN- γ expression, which are implicated in allergic pathways, suggest a systemic defect in DC programming

in AR, leading to their aberrant potential to induce Th2/Th17-cell polarization, a driver of autoimmunity. An animal study demonstrated inhibition of allergic airway inflammation by suppressing the formation of inflammatory DC at the inflammatory site(67).

Mast cells and basophils have come into attention as their roles in allergic diseases are increasingly defined(68-70). Basophil activation parallels immediate allergic reactions and CD63, a membrane protein from histamine-containing lysosomes, is upregulated during basophil activation. The basophil activation test (BAT) is increasingly utilized as a measure of allergic activity, following increasing ubiquity of flow cytometers. EAACI recently issued a Position Paper on the utility of BAT in allergic diseases(71). BAT is a functional *ex vivo* test that can negate the risks of *in vivo* provocation tests. It can be used to diagnose allergies to common allergens, drugs, venom, and autoimmune urticarial, monitor the severity and resolution of allergic conditions, and the effects of immunotherapy. More research on the standardization of values and cost-effectiveness of BAT are needed.

There are suggestions that allergic response could be influenced by the circadian rhythm (68). Ando et al. demonstrated that allergen-induced surface CD203c expression on basophils in seasonal AR is varies with the time of the day and is associated with temporal variations in circadian Clock gene expression(72). Recently, Nakao et al. have reviewed systemically circadian clock functions and suggested that research on how time of day impacts allergic reaction, which we may call 'chronoallergology', will provide exciting insights into previously unknown aspects of the biology of allergies which may initiate novel strategies for management of these diseases(73).

NAC is widely used to directly evaluate the sensitivity of the nasal mucous membrane to allergens, mediators of Type I allergy, and drugs. Agache et al. have recently published a position paper that appraised NAC methods, and provided recommendations on indications and safety(49). Shamji et al. have confirmed systemic cellular activation (e.g., basophils, T-cells, and dendritic cells in peripheral blood) following a NAC(74). Airway epithelial cells are known to be the primary site encountering aeroallergens, they have also an important role in the modulation of allergic inflammation responses(75). Segboer et al. found a high prevalence of hyper-reactivity in both AR and NAR (>60%) during cold dry air provocation, which triggered rhinitis symptoms and increased nasal secretions in these patients but not in controls(76). They concluded that AR and NAR could not be distinguished by response to nasal stimuli.

TREATMENT OF AR

Symptoms of AR and CRS are both manifestations of inflammatory reactions of the nasal and sinus mucosa. The notion of “control” is a key concept in the management of these conditions, as the realistic goal for the majority of patients is “control” rather than the elusive “cure”. Hellings et al. performed a review on uncontrolled AR and CRS in which they determined four major contributory factors to uncontrolled AR and CRS; such as disease-related factors (SCUAD, endogenous, exogenous and genetics factors), diagnosis-related factors (misdiagnosis, concurrent local or systemic diseases), patient-related factors (compliance), and treatment-related factors (inadequate treatment and symptom control)(77). This review emphasizes the need for refining the definition of disease control and proposed thorough assessment and management based on the four above-mentioned factors. Recently, Papadopoulos et al. proposed a new stepwise management approach of AR based on control that can be based on a number of criteria , including a patient-reported metric of quality of life, symptoms, objective measurements, and an easily applied test to evaluate nasal patency(78).

1. Immunotherapy

Immunotherapy (IT) is the only disease-modifying treatment modality that offers sustained symptomatic relief even after cessation of therapy(79). IT can be administered subcutaneously (SCIT) or sublingually (SLIT). In support of the efficacy of IT, Scadding et al. performed nasal allergen challenges in patients receiving timothy grass pollen IT (SCIT or SLIT), and showed blunted clinical and immunological responses to allergens in IT-treated patients(80). SLIT decreased IL-4 levels and mIL-4 receptors and increased inhibitory IL-4 receptors (81), and desensitization reduced basophil response rapidly and non-specifically at a stage before p38 MAPK phosphorylation(82). Recently, the EAACI Task Force recommended a standardized method for outcome measures in nine domains, including total symptom scores, medication score, combined symptom medication score, health-related quality of life, visual analogue score, well and severe days, global assessment and patient satisfaction, rhinitis control, and allergen provocation tests (83). The decision on IT initiation should be based on evaluation of existing medical conditions and a risk/benefit assessment for each patient(84). Other IT products (both in SLIT and SCIT) using recombinant Bet v 1 have been evaluated by its safety and efficacy in randomized clinical trials (85, 86). Senti et al. presented a summary of three clinical trials using epicutaneous allergen immunotherapy that has shown amelioration of hay fever symptoms and good safety profiles(87)

IT may result in allergic reactions especially during initiation of therapy. This is of particular concern in asthmatics. Sastre et al. reported a significant association between the number of grass allergens patients are sensitized to and the number of adverse reactions to IT (88). However, in an analysis of 3314 adults and 881 children on Timothy grass SLIT, Maloney et al. found no evidence of increased frequency for treatment-emergent adverse events, systemic allergic reactions, or severe local allergic swellings in adults or children with asthma treated with grass SLIT tablet versus subjects without asthma in or outside of pollen season (89).

Many AR patients are polysensitized. The efficacy of single-allergen IT in polysensitized patients is under debate(79). However, clinical trials that evaluate the efficacy of mixed allergen extracts in IT are in want. A randomized placebo-controlled trial by Nelson et al. using grass IT tablets found similar improvements in symptoms scores and favourable safety profile in both mono- and polysensitized patients(90). O. Pfaar et al. conducted a multicentre, double-blind, placebo-controlled trial of SCIT with mixed depigmented-polymerized birch and grass pollen extract in 285 patients with allergic rhinoconjunctivitis and demonstrated significant reduction of combined symptom and medication score and the rhinitis quality of life questionnaire with the SCIT-treated group, compared to the placebo group(91).

While the use of IT is increasing, there are no universal standardization for the dosage and preparation of IT agents, with different manufacturers employing different dosages, compositions and reference units. While the CREATE project provides standards for specific IT materials, it is not all-encompassing(92). Benitez et al. analysed the constituent HDM allergens and their concentrations in five SLIT products in Spain and found substantial variations in allergen content among these five products(93). In their study, *Der p* 1 concentrations ranged from 0.6 to 14.5 µg/ml (24-fold difference); similar figures were found for *Der f* 1 that ranged from 0.2 to 12.4 µg/ml (62-fold difference). *Der p* 2 + *Der f* 2 ranged from 0.2 to 1.5 µg/ml (7.5-fold difference). The fact that allergen concentrations varied so significantly in these products is alarming. This highlights the need for more stringent testing on the appropriate concentrations and types of allergens in IT products.

2. Second-generation H₁-Antihistamine

Second-generation antihistamines are recommended by guidelines for AR as they are safe and efficacious(1, 94, 95). Mullol et al. reviewed the evidence for Rupatadine in 2008, in which its efficacy and safety were established(96) and in 2015(97), for its properties as antihistamine and platelet activating factor (PAF) respectively. PAF is a phospholipid-derived mediator found primarily in mast cells and is involved in eosinophil chemotaxis and degranulation via G-protein coupled PAF receptors, and mast cell degranulation(98, 99). PAF is a key mediator of mucosal inflammation in AR and the wheal and flare reaction in urticaria(100, 101). Bilastine, a new H₁-antihistamine approved for rhinoconjunctivitis, has shown efficacy that increased with up-dosing but without sedation in the treatment of cold contact urticaria(102).

3. Acupuncture

Choi et al. found that TNSS was significantly reduced in the group that received 4 weeks of acupuncture compared with the sham acupuncture (difference = -1.03) and observation groups (difference= -2.49)(103). However, outcomes were based on self-reported questionnaires and not objective outcomes.

4. Novel targets for therapy

The EAACI Interest Group on biologicals published a review on the use of biologic agents in allergic disorders, including agents targeting IgE, Th2-type and Th2-promoting cytokines, pro-inflammatory cytokines, chemokine receptor CCR4, and lymphocyte surface and adhesion molecules. The integration of information in this review helps readers understand these new therapeutic agents (104).

Von Gunten et al. conducted an excellent review of the mechanisms and potential therapeutic targets for allergic inflammation(105). In addition, KleinJan et al. found that topical application of a sphingosine-1-phosphate (S1P) analogue (FTY720) to allergen-sensitized mice resulted in decreased eosinophils, mast cells and dendritic cells in nasal mucosa. IL-4, IL-5, IL-10 and IL-13 production also fell significantly(106). Targeting Notch signaling pathways may also provide an inhibitory effect on GM-CSF priming-induced transendothelial migration of human eosinophils which is a significant pathological feature in allergic inflammation(107).

Fonseca et al. demonstrated the promising potential of mycobacterial antigens for clinical trials(108). Their data suggested that MyD88 signaling could be a common pathway in the distinct mechanisms of therapeutic efficacy of allergen-free immunotherapy. During immunotherapy with CpG/CFP, IFN- γ secretion induced via MyD88 signaling could reverse the allergic response by downregulating Th2 cells. In addition, immunotherapy with CpG/CFP activates non-apoptotic Fas signaling, and possibly reduces allergic response via IFN- γ and IL-10 production(108). Pollen-derived adenosine is a critical cofactor in ragweed-pollen induced allergic airway inflammation and may highlight adenosine receptors as potential drug targets (39).

The CRTH2 antagonist OC000459 was found to be a safe and effective oral anti-inflammatory agent, which achieved clinically meaningful improvements in lung function and asthma control in allergic asthmatics(109) and clinical benefits in eosinophilic oesophagitis(110). A small randomized crossover study using OC000459 showed significant and persistent reduction in rhinoconjunctivitis symptoms compared to placebo(111). While OC000459 shows promise in AR, larger studies are required to demonstrate its efficacy and safety profile.

NOVEL USE OF INFORMATION TECHNOLOGY

The increasing penetration of the internet and smartphones has led to opportunities for the medical and scientific professions to have remote access to patients, provide instant information to patients and have real-time information about patients' medical conditions.

Kang et al. found a high coherence between (i) search volume of AR-related words (eg. “pollen count”, “cetirizine”, “loratadine”), (ii) antihistamine sales and (iii) pollen counts(112). Pollen seasons correlated strongly with peaks of AR-related search volumes and antihistamine sales data. Google Trends, a surveillance tool that allows for the study of trends of searches on Google, has proven effective in predicting influenza outbreaks. Big data on epidemiology will likely play a more significant role in the management of allergy.

de Weger et al. tracked AR symptoms by having a large number of Dutch volunteers report regularly their location and symptoms onto the study website(113). Symptom scores correlated significantly with (i) pollen concentrations, (ii) self-reported allergen sensitivity profiles, and (iii) antihistamine sales. Remote self-reported symptoms can provide location- and time-specific epidemiological information of AR.

GA2LEN harnessed information from patients’ Hay Fever Diary, pollen concentrations from the European Allergen Network, and air quality and pollen concentration forecasts from across Europe (SILAM Network) to determine the pollen concentration that triggered symptoms for individual patients. By determining the individual threshold pollen concentration, patients can be informed in advanced when pollen concentration reaches their threshold and hence manage their symptoms better. In a position paper by MACVIA-ARIA Sentinel Network for allergic rhinitis (MASK-rhinitis), the use of electronic reporting of daily symptoms during pollen season via mobile devices in 13 European countries was described(114). This information was processed by a clinical decision support system. The data can be used to provide patients and the public with advice during pollen season and is useful for research and climate evaluation purposes.

SUMMARY

The diversity of research and the strides we are making in the understanding and management of AR is both encouraging and humbling. The challenge for clinicians and scientists like ourselves lies in keeping abreast of these research findings and the latest clinical guidelines. We hope this review has summarized, in a succinct and contextualized manner, the new information available. Readers are directed to the referenced articles that are of interest to them for full information.

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Figure 1. Summary of risk factors for allergic rhinitis and allergic sensitization published in *Allergy* journal (2013-2015)

