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ABSTRACT

Allergic rhinitis (AR) is an upper airway disease with high prevalence in the world, and therefore needs to be thoroughly investigated and treated accordingly. Although the mechanisms underlying the pathology and treatment of AR have been widely studied, many aspects of AR are still unclear and warrant further investigations. The purpose of the present review was therefore to report recently published papers, which highlight the novel mechanisms and treatments of AR. These include role of environment, important proteins and cells, and some other factors in the pathogenesis of AR; as well as the role of immunotherapy and biologics in the treatment of AR.

KEY WORDS

Allergic rhinitis, Biologics, Mechanisms, Treatment

INTRODUCTION

Allergic rhinitis (AR) is an upper airways disease, characterised by symptoms of nasal obstruction, rhinorrhea, sneezing, and nasal pruritus caused by inhaled allergens and involving mucosal inflammation. Although the mechanisms underlying the pathology of AR have been widely studied, the in-depth mechanisms remain to be further investigated. Similarly, although

several treatments are available for the management AR, some have not been found to be efficacious in all patients, and thus led to development of novel therapies. The aim of this review is to highlight the recent advances and novel developments in AR.

ENVIRONMENTAL FACTORS

Allergic rhinitis (AR) is one of the most common diseases in the world, with an incidence of 10% -40% in the population (1). The clinical symptoms include nasal obstruction, rhinorrhea, nasal itching, sneezing and nasal itching (1). Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have classified AR as either an intermittent disease based on the presence of symptoms of AR for less than 4 days a week or less than 4 weeks; or as a persistent disease based on symptoms lasting for more than 4 days a week for more than 4 weeks(1). On the other hand, AR can be divided into seasonal AR (SAR) and perennial AR (PAR) based on the type of allergens. In this regard, outdoor allergens, such as grass and tree pollens, are normally the main sensitizing allergens for SAR, whereas indoor allergens, such as dust mite allergens are the sensitizing allergens for PAR (1, 2). Recent studies have found different allergens to be prevalent in different regions. For example, birch and grass pollen are the two most common allergens in Denmark (3), Japanese cedar pollen (JC) is most common in Japan (4, 5), and artemisia pollen is the main allergen in northern China (6). In some regions, ragweed is the most common sensitizing allergen (7). Thus, based on the evidence from these studies, it is necessary to determine the appropriate allergens to define AR and confirm the diagnosis of AR to the allergen/s using corresponding nasal allergen challenge tests (8-10). Moreover, as differences in the environment and the allergens in different regions are likely to impact the clinical diagnosis of patients with AR (11), this may consequently lead to differences in AR prevalence. For instance, the prevalence of AR is high and on the rise in Japan and Inner Mongolia in China (5, 12, 13).

The prevalence of allergic diseases has also been found to be different in urban and rural areas. For example, a more recent study assessing the relationship between environmental and dietary factors and allergic diseases in urban and rural children in South Africa showed that exposure to farm animals during pregnancy had a protective effect against allergic outcomes in infants and

their mothers in rural populations (14). In urban children, caesarean section was associated with food allergy, and consumption of fermented dairy products was associated with reduced asthma and atopic dermatitis(14). Sometimes, environmental factors may not only induce AR, but may also aggravate AR (2). In particular, an increase in air pollutants in the environment has been found to be associated with increased incidence of allergic respiratory diseases (15); with one study in children demonstrating that exposure to oxidizing pollutants in the air leads to a higher risk of developing AR in these children (16). There is evidence that exposure to the particulate matter (PM_{2.5}) in the environment may increase the degree of DNA methylation in the body (17). Furthermore, environmental factors can also lead to phenotypic genetic changes that promote the increase in allergic diseases (18).

MECHANISMS

Proteins

The association between certain proteins and AR has received much attention recently. Some studies have shown increased epithelial permeability and defective epithelial barriers in patients with AR, with histone deacetylase (HDAC) activity considered to be an important driver of allergic inflammation and tight junction dysfunction (19). It has been suggested that increased HDAC activity may be an important mechanism underlying airway epithelial tissue and cell damage, and that blocking HDAC activity may restore the integrity of the epithelial barrier (19). The lack of mucin 1(MUC1) has also been shown to promote nasal epithelial barrier dysfunction in patients with AR (20). There is evidence that severe dysfunction of the epithelial barrier may allow allergens to enter the submucosa easily, resulting in the activation of monocytes and subsequently triggering a series of allergic reactions (10). The immunoglobulins (Ig), particularly IgE, also play an important role in the pathogenesis of various allergic diseases (21). One recent study has proved that the frequency and function of circulating T cells in patients with AR were inversely related to antigen-specific IgE levels and disease severity (2, 22). More recently periostin has also been suggested to be important in AR. It can transduce allergic diseases through a series of signals and can be secreted with mucus (23). Thus, some studies have suggested that

periostin might also be useful as a new biomarker of allergic diseases (23, 24). Similarly, as C-reactive protein levels have been shown to be elevated in obese subjects, it is possible that C-reactive protein may also have an underlying inflammatory role in AR (25).

Cells and cytokines

Besides the important proteins mentioned above, several cell types and inflammatory mediators have been shown to be involved in the development of allergic rhinitis (Figure 1). It has been reported that type 2 innate lymphoid cells (ILC2s), especially myeloid dendritic cells (mDC) and plasmacytoid dendritic cells (pDC), play an important role in allergic diseases (26). Although the association between dendritic cells and interleukin-2 (IL-2) in allergic diseases, especially AR, is still unclear, a recent study has shown that while myeloid dendritic cells can promote IL-2 function via IL-33/ST2 (growth STimulation expressed gene 2) pathway, activation of pDC actually inhibits IL-2 function through IL-6 pathway (27). Other studies have shown that the expression of Cysteinyl leukotriene receptor type 1 (CysLT1) is increased on ILC2 in AR patients, and CysLT1 antagonists can affect ILC2 activity (28). Furthermore, homologous and autogenous mDCs can activate ILC2s in AR patients to produce T helper 2 cell (Th2) cytokines (27), likely via subsequent activation of eosinophils, B cells, mast cells, macrophages, fibroblasts and epithelial cells, which results in initiation and maintenance of airway inflammation (29). Thus, collectively these studies indicate that ILC2s are an important component of the Th2 innate immune response in airway inflammation. Indeed, the ILC2-mediated immune microenvironment is characterized by the production of IL-4, IL-5, IL-9, IL-13, IL-25 and IL-33 by Th2 cells, mast cells and histiocytes(27).

A more recent study investigating the prevalence of ILC2s in inferior nasal turbinate tissues and the activating mechanisms of ILC2s in patients with house dust mite (HDM)-induced AR showed that prostaglandin D2 (PGD2) and cysteinyl leukotrienes (CysLTs)-induced the production of IL-5 and IL-13 from ILC2s; which could completely be inhibited by ramatroban, a dual chemoattractant receptor homologous molecule of Th2 cells (CRTh2) and thromboxane receptor antagonist, and montelukast, a CysLT1 antagonist, respectively (30). The authors suggested that

PGD₂-CRTh2 and cysLTs-CysLT1 axes may play an important role in activation of tissue-resident ILC2s to produce Th2 cytokines, leading to the development of allergic inflammation in AR (30). Indeed, CysLT is an effective inflammatory mediator that promotes the occurrence of SAR (31). One recent study has investigated the relationship between epithelial fucosylation and innate allergic airway inflammation in mice, particularly as lung epithelial cells have been shown to be heavily fucosylated by fucosyltransferase (FUT) 2 in house dust mite (HDM)-induced asthma model and the development of allergic inflammation is attenuated in FUT 2-deficient animals (32). The authors further demonstrated that FUT 2-mediated fucosylation of epithelial cells led to the local production of complement 3a (C3a). Furthermore, in the airways of mice lacking FUT 2, decreased C3a production led to a decrease of IL-33-induced inflammation and accumulation of ILC2s (32). A gradual development of a regulatory T cell (Treg) response was also confirmed. In patients with AR, nasal allergen stimulation has been shown to reduce the peripheral blood ILC2s (33), confirming that Th2 cells and eosinophils are important factors of innate allergic inflammation (34, 35). At the same time, a survey found that about 52% of allergic rhinitis subjects released extracellular vesicles, because they contain complex bioactive molecules, and participate in intercellular communication according to the specific IgE of grass pollen (36) mediated by mast cell activation specific IgE (37). For example, immune complexes exposed to extracellular mast cell nanovesicles can amplify allergic inflammation (38), which also supports this view.

Other risk factors of AR

Besides the factors mentioned above, some other factors may also play important roles in AR (39, 40). Clinically, AR patients with asthma are more difficult to treat (40). In terms of genetic factors, up to 160 AR susceptible loci have been found in recent genome-wide association studies (GWAS) studies; with most of these genes being enriched in cytokines and immune regulatory pathways. Although genetic sites of AR share the same genetic basis with asthma and allergic dermatitis, AR also has its own genetic susceptibility sites, reflecting the specificity of different tissues to allergens (41-43). Age also has an important impact on AR. Intrauterine growth

restriction has a protective effect on human allergic diseases, and foetal oxidative balance (protective prenatal factors counteract oxidative stressors) may play a key role in the prevention of asthma and allergic diseases (44). Children born by caesarean section, and especially those by midwife-assisted birth, may have a higher risk of asthma and sensitization in childhood (44). Prenatal protective nutrition (vitamin D and polyunsaturated fatty acids (PUFAs)) can also improve the risk of asthma and allergic diseases in adolescents (45). DNA methylation, an important epigenetic mechanism involved in transcriptional regulation, has also shown to be associated with allergic sensitisation. A recent longitudinal study investigating genome-wide DNA methylation in peripheral blood of pre- and post-adolescent individuals found that methylation at 33 cytosine-guanine sites (CpGs) was associated with AR; of which methylation at one particular site (cg10159529) was strongly correlated with IL5a gene expression, and methylation at three other sites (cg14121142, cg23842695, and cg26496795) was associated with AR sensitization in age-specific manner (46). Indeed, many adolescent individuals are asymptomatic and develop AR in adulthood (47). Diet is also related to AR, and studies have indicated that dietary changes can lead to increased incidence of allergic diseases and asthma (48). Similarly, changes in environmental factors, such as temperature and climate change, can lead to changes in allergens such as pollen, which can induce or aggravate the symptoms of allergic rhinitis (49).

TREATMENT

Management of AR includes patient education, pharmacotherapy, allergen-specific immunotherapy (AIT) and biologics (17). Some novel treatments for AR are summarized in Table

1.

Patient education

AR severely impacts the Quality of life (QoL) and sleep, leading to anxiety and depression (50). Clinically, some doctors tell patients what to do but not why to do it. Patients' inadequate understanding of their treatment options contributes to poor compliance to some extent. Therefore, doctors should tell patients the different treatment options, including details of route of

administration and benefits and risks of existing treatments, and involve patients in decision-making (51). Furthermore, patients need to understand how drug/s work to take medication regularly (52). If patients participate in their own treatment and fully understand the treatment plan, the compliance will improve.

Mobile health technology can improve patients' treatment compliance by reminding them to take medications as necessary and recording drug intake (53, 54), which is important for older patients or busy patients, because it can help them to take medications regularly to improve the effectiveness of treatment. In this regard, the Mobile Airways Sentinel Network (MASK) study has recently investigated the incidence and control of daily allergic multimorbidity and its impact on work productivity in a cohort of 4210 users in 19 countries, using a mobile phone app (Allergy Diary) to collect visual analogue scales (VAS) data and demonstrated that work productivity was correlated with VAS global measured levels and with multimorbidity patterns (54). Furthermore, pilot MASK study has additionally assessed the real-life treatment of allergic rhinitis in 2871 patients using a treatment scroll list including all medications prescribed and over the counter (OTC) for rhinitis customized for 15 countries (55). This study demonstrated that patients tended to increase treatment use with the loss of symptom control other than a daily basis. The Allergy Diary further allowed differentiation between treatments within or between classes (intranasal corticosteroids and oral H1-antihistamines); thus, confirming the usefulness of the Allergy Diary mobile app in assessing daily use in AR (55).

Pharmacotherapy

The pharmacotherapy of AR includes nasal/oral glucocorticoids, antihistamines, leukotriene receptor antagonists, mast cell membrane stabilizers, decongestants and anticholinergic drugs (17). There are several advances in pharmacotherapy. In a guinea pig allergic asthma model, inhalation of the arginase inhibitor 2(S)-amino-6-boronoheptanoic acid (ABH) was shown to reduce airway hyperresponsiveness (AHR) and protect against allergen-induced early and late asthmatic reactions and airway inflammation (56). Although there have been no human trials, these findings suggest that ABH may be used to promote the treatment of asthma and AR in the future.

As L-arginine is a common substrate for both arginase and NO synthase activity, it has been suggested that inhibition of arginase may lead to increased metabolism of L-arginine via NO synthase and resulting in increased synthesis of NO, which is also known to induce bronchodilation, and inhibit airway inflammation and release of mast cell mediators (56). Similarly, MP29-02, a combination nasal spray of azelastine hydrochloride (AZE) and fluticasone propionate (FP), has been shown to reduce inflammatory mediators and nasal hyperreactivity (NHR) in AR (57). In addition, Yu et al found that glucocorticoid can decrease the ILC2s levels in asthma patients and asthma with AR patients via MEK/JAK-STAT pathways (26), which was a new discovery of glucocorticoid in the treatment of asthma or AR.

Allergen-specific immunotherapy

Although allergen-specific immunotherapy (AIT) is the only treatment that targets the underlying pathophysiology and alters the natural history for AR, there's much room for improvement in allergen immunotherapy guidelines (AIT-GL) (58). The efficacy of AIT has been documented in several randomized controlled trials, meta-analyses and systemic reviews (59-62). However, the long lasting medication time may be a drawback of AIT. One study showed that two years of treatment was effective but not long enough to lead to long-term tolerance, and that Th2 cell response paralleled the transient clinical outcomes, while IgE blocking antibody persisted constantly (63, 64). Also, AIT faces several challenges, such as worldwide standardization, occasional severe side effects, low patient adherence, and high costs over long periods (65). Similar to adult patients, AIT is efficacious in paediatric patients as well and there is some evidence of AIT preventing progression of AR to asthma (21). Overall, AIT provides real world benefits of long-lasting effect after treatment cessation as a consequence of significant reduction in the use of medications for AR and asthma (36, 66, 67) and a reduced risk of asthma (21, 67).

AIT medications: To date, crude allergen extracts, purified or recombinant allergens and modified allergens like allergoids, purified peptides and new adjuvants have been employed in AIT (68). In this regard the recombinant B-cell epitope-based grass pollen vaccine BM32 (69) and the Lolium perenne peptides (LPP) (70,71) have been shown to be effective, safe and well-tolerated in

treatment of allergic rhinitis. The main disadvantage of LPP is that the risk\benefit balance of particularly LPP-SCIT remains to be fully evaluated in large numbers of allergic rhinitis patients, however, available data suggest that short-term SCIT with LPP may lead to greater compliance and efficiency, as well as fewer systemic reactions and late-phase skin reactions due to low cross-linking with high-affinity IgE receptors, compared to standard SCIT using conventional whole allergen extracts (70, 71). Furthermore, it has been suggested that based on the extensive immunological cross-reactivity among grass pollens belonging to different species, L. perenne-derived allergens might be considered appropriate for the treatment of IgE-mediated grass pollen allergy in general (72).

Routes of administration: Several approaches have been tested for administration of allergen in AIT, including the traditional subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) approaches, and novel approaches like intradermal, epicutaneous, intra-lymphatic or intranasal (29). With intra-lymphatic immunotherapy (ILIT), it is possible to complete the entire treatment within 2 months, whereas SLIT and SCIT generally require treatment periods of approximately 3 years (29). While persistence and adherence to AIT medication has been shown to be similar for SLIT and SCIT, SLIT is more common due to lower risk of anaphylaxis and serious adverse reactions, as well as ease of administration, and thus more patients are willing to initiate treatment (73). Although patients receiving SLIT frequently discontinue earlier in the first year compared to patients receiving SCIT, possibly due to adverse oral effects, more of the patients persisting with SLIT are more likely to go into year 3 treatment compared to those on SCIT (73).

Biomarkers of AIT efficacy: As biomarker/s of effective clinical response to AIT would help to monitor the efficacy and control the disease (29), finding such biomarkers has attracted much attention (70). Recent studies have demonstrated novel mechanisms underlying the efficacy of AIT. One study has indicated that AIT upregulates activated allergen-specific Treg cells, and downregulates dysfunctional Treg cells (73). Furthermore, increased allergen-specific IL-22-secreting CD4⁺ T cells can relieve allergic symptoms by inducing increased

allergen-specific IL-10-secreting Treg cells (73). Allergen-reactive ST2⁺CD45RO⁺CD4⁺ cells or cells combined with IL-5⁺IL-13⁺CD27⁻CD161⁺ CD4⁺ cells may be useful markers of AIT as they have been shown to be significantly decreased after SLIT (74). While acquisition and maintenance of activated memory regulatory T (am Treg) cells may be important in sustaining the anti-allergic effect after cessation of AIT (75), another study has suggested that memory B cells expressing IgG2 or IgG4 may also play a role, as these are increased following allergen immunotherapy (76). Allergen-sIgG4 antibody may be a novel biomarker through increasing in nasal fluid after SCIT (77) and IL-10 gene expression levels in whole blood may be a predictive biomarker in patients accepting sublingual HDM AIT (78).

Biologics

Presently there are many type 2-targeting biologics, such as omalizumab (anti-IgE mAb), mepolizumab and reslizumab (anti-IL-5 mAb), benralizumab (anti-IL5Ra mAb), and dupilumab (anti-IL4Ra mAb) (79, 80); and of which omalizumab and dupilumab have entered the market (81). A randomized, double-blind, placebo-controlled, parallel group, pivotal phase 2b clinical trial has demonstrated that dupilumab 300mg q2w, as a supplement therapy to medium-to-high-dose inhaled corticosteroids (ICS)+long-acting β 2-agonists (LABA), can relieve nasal symptoms in patients with uncontrolled persistent asthma and comorbid PAR (82). Indeed, Bachert and colleagues (83) have shown that adding dupilumab to intranasal corticosteroids (INCS) also reduced disease severity and improved the QoL of adults with chronic rhinosinusitis with nasal polyps (CRSwNP), a type 2-mediated nasal inflammatory disease similar to AR. Studies investigating the effect of omalizumab have demonstrated that while intranasal administration of omalizumab did not increase the level of allergen-specific or total IgE, subcutaneous administration of omalizumab caused significant increases in total IgE and IgE-omalizumab complex (84). It is likely that IgE-omalizumab complex increases the half-life of IgE, rather than increasing IgE production, resulting in an increase in total IgE levels. Fel d 1, a major cat allergen triggering asthma and rhinitis, has been shown to be neutralized by addition of anti-Fel d 1 IgY into cat food, thus reducing active Fel d 1 in cat saliva and shed hair and dander,

leading to reduced symptoms in cat-sensitized individuals (85). This broke the stereotype of people using drugs to control their AR or asthma symptoms. By adding anti-Fel d 1 IgY to cat food, the production of Fel d 1 can be reduced, which can not only enable AR patients to keep cats, but also control the frequency and severity of symptoms without medication.

CONCLUSION

AR is an upper airway disease with high prevalence worldwide. As an increasing number of studies have focussed on the mechanisms underlying the development of AR, the importance of several novel and complex pathways has become clearer. Recent developments have highlighted the role of different environmental allergens and triggering factors in influencing differences in the prevalence and management of AR in different parts of the world. This review has further highlighted the role of proteins such as HDAC and MUC1 in the integrity of epithelial tight junction barrier, and that ILC2s are a vital component of the Th2 innate immune response in AR. Novel therapies such as highly purified allergen extracts and purified or recombinant allergens, allergoids, peptides and new adjuvants for use in specific allergen immunotherapy and specific monoclonal antibodies (biologics) for blocking the effects of IgE, IL-4/ IL-5 and/or their receptors were also reviewed. The new findings reported in this review undoubtedly increase our understanding of the mechanisms involved in the aetiology of AR, and might help in optimizing the management of AR, and possibly other allergic diseases, in terms of timing of intervention with optimal pharmacologic and other therapeutic approaches.

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TABLES

Table 1. New treatments under investigation/development for allergic rhinitis.

Interventions	Tools/Drugs	Description	Administration route	References
Patients' education	MASK-Allergy Diary	-	Smartphone/Internet	(53-55)
Pharmacotherapy	ABH	arginase inhibitor 2(S)-amino-6-boronohexanoic acid	Inhala	(56)
	MP29-02	combination nasal spray of azelastine hydrochloride and fluticasone propionate	Intranasal	(57)
Allergen immunotherapy	Subcutaneous immunotherapy	lolium perenne peptides/ recombinant B - cell epitopes	Subcutaneous	(69-72)
	Sublingual immunotherapy	Grass allergen peptide /house dust mite tablet	Sublingual	(62, 76)
	Intralymphatic immunotherapy	extracts of grass and birch pollen, house dust mites, dog or cat allergen	Intralymphatic	(29)
Biologics	Omalizumab	Anti-IgE	Subcutaneous	(79-81)
	Dupilumab	Anti-IL4R α	Subcutaneous	(79-83)

FIGURE LEGENDS

Figure 1. Schematic diagram of the mechanisms underlying pathogenesis of allergic rhinitis: including the interaction between proinflammatory cytokines, inflammatory cells, and environmental and genetic factors. (DC = Dendritic cell; EOS = eosinophil; BAS = basophil; Ig-E = immunoglobulin E; IL = Interleukin; ILC2= Type 2 innate lymphoid cell; MC = mast cell; Th2 = T-helper Type 2 cell; TSLP= Thymic stromal lymphopoietin)

