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Therapeutic Strategies towards Allergic Diseases

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Abstract

Allergic disease is a prevalent clinical and public health problem, and is among the most common health issues worldwide. The therapeutic strategies include two major categories: allergen-specific immunotherapy (AIT) and non-specific therapies. AIT is associated with improved tolerance to allergen challenge, with a decrease in immediate-phase and late-phase allergic inflammation. Despite its clinical practice for nearly a century, allergen extracts retain the risk of IgE-mediated allergic responses. Over the years, the epitope complexity of natural allergen extracts can be recreated using recombinant proteins, and more rational and safer preparations are appearing. Non-specific therapies mainly target the IgE-FcεRI interaction, as well as mast cells homeostasis or the multiple biological mechanisms of allergy. Nevertheless, the diseases sometimes remain un(der) diagnosed and inadequately treated. Continued experimental studies are crucial to develop new treatment approaches, as well as reliable biomarkers. And the guidelines of allergy medication has so far failed to be well implemented. Therefore, we summarize the latest advances of therapeutic alternatives involved in allergic diseases to offer clinicians a clearer understanding of the proposed therapeutic recommendations in order to use this knowledge to develop individualized treatment plan.

Keywords

Allergic disease, Medication, Treatment, Therapy

Introduction

Allergic diseases that comprise food and drug allergy, allergic rhinitis, asthma, urticaria and atopic dermatitis exhibit the complexity of broad disease spectrum and affect 20-30% of the world population [1]. They have a negative impact on the quality of life and sometimes lead to life-threatening events such as fatal asthma and anaphylaxis [2]. Because of the various underlying molecular mechanisms, there are no established methods to prevent them. Evidence shows the role of diet as a factor influencing immune homeostasis and the development of allergic diseases [3]. ω3 polyunsaturated fatty acids (PUFAs), vitamins and fiber have been shown to exert anti-allergic effect, and protect against allergic diseases [3,4]. Genome wide association study defined gene region such as DPP10, PCDH1, NPSR1, PHF11, PLAUR, ADAM33 and HLA-DR are probably associated with significant genetic risk for allergy [5,6]. In predisposed individuals, initial exposures to allergens lead to the activation of $CD4^+$ T helper 2 (Th2) cells and the production of Th2 cytokines IL-4 and IL-13, which allows isotype switching of B cells to generate specific IgE antibodies. IgE binds with FcεRI (high affinity receptor for IgE) expressed on the surface of mast cells or basophils, which is known as allergic sensitization. Crosslinking of FcεRI by allergens leads to tissue resident mast cell activation and degranulation [7]. Mast cells have the ability to cause profound inflammation and vasodilation upon the release of preformed mediators, as well as subsequent synthesis of new inflammatory mediators. The release of histamine, lipid mediators, chemokines and cytokines causes immediate allergic symptoms. The mediums mostly have blood vessel activity, which can increase vascular permeability and promote local or systematic allergic inflammation reactions. The subsequent presentation of allergen-derived peptides by antigen-presenting cells (APCs) to allergen-specific $CD4^+$ T cells activates the production of pro-inflammatory cytokines, which drives the late chronic forms of allergic inflammation [8].

As we all know, allergen sensitization is fundamental in the development of allergic symptoms. Therefore, elimination or avoidance of the specific stimulus or antigens before or after sensitization should be beneficial. Current therapies for allergy focus on controlling symptoms, and they do not change the recurrent course of disease. Several treatment guidelines have been established and updated repeatedly. However, the adherence to these evidence-based treatment guidelines was low. Although the molecular mechanisms associated with allergy have been extensively studied, we currently lack countermeasures to the better control of severe forms of allergic diseases and the development of curative therapies. To fill this gap, it will be necessary to piece together individual research to form an overview of the treatment strategies that are now appearing on the horizon. In this review, we highlight the current interventions, as well as possible innovative immunological and molecular approaches for allergic diseases including therapeutic antibodies, cytokines, small molecules and soluble receptors.

Established Treatment Guidelines

In 2001, allergy researchers from many countries published a consensus guideline, "Allergic Rhinitis and its Impact on Asthma (ARIA guidelines)" with WHO's recommendation. Other guidelines such as GINA for asthma, and EAACI/GA2LEN/EDF/WAO for urticaria, were also established and have been evaluated over these years. They not only cover the definition and classification of the

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corresponding disease, but also provides assessment of disease activity and the recent progress in identifying its pathogenic mechanisms. Most importantly, these guidelines outline diagnostic and therapeutic management for different types of allergic diseases [9]. According to guidelines, management of most common allergic diseases generally relies on pharmacotherapy to decrease pathological symptoms. However, they only temporarily alleviate symptoms and suppress allergic inflammation responses.

Chemical mediator receptor antagonists

Many symptoms of allergic diseases are mediated primarily by mast cell mediators, such as the actions of histamine on H1-receptors located on endothelial cells (the wheal) and on sensory nerves (neurogenic flare and pruritus). H1-antihistamines stabilize histamine H1-receptors in an inactive state, and thus reduce the effects of histamine on the target organs. Although the early products (e.g. diphenhydramine, ketotifen and chlorpheniramine) were effective at controlling the symptoms of allergy, their sedative and anti-cholinergic side-effects on the central nervous system were problematic [10]. Modern second generation H1-antihistamines (e.g. cetirizine , loratadine, and acrivastine) are minimally or not sedating and free of anti-cholinergic effects, and are the first line agents used to treat urticaria because of their good safety profile. They are recommended to be preferred over first generation H1-antihistamines, even up to an increase in the dose to fourfold [9,11].

In contrast to histamines, Leukotrienes such as LTC4 and LTD4, which are also released by mast cells after activation, have potent relaxing effects on vascular smooth muscles, enhancing vascular permeability and vasodilation, and stimulating eosinophil migration, which cause mucosal swelling, rhinorrhea and nasal congestion. Leukotriene receptor antagonists (antileukotrienes) such as Pranlukast and Montelukast are available on the market. They are more effective for nasal blockage than second-generation antihistamine [12]. However, for adults and children with chronic rhinosinusitis without nasal polyps, antileukotrienes are not recommended [13]. Prostaglandin D2 and thromboxane A2 receptor antagonists also suppress the vascular permeability of the nasal mucosa, and improve nasal blockage. However, their effects are relatively slow, and may lead to bleeding tendency [12].

Glucocorticosteroids

Besides histamines, other mast cell mediators such as PAF, leukotrienes, cytokines and bradykinin are also involved in allergic diseases and lead to a pronounced cellular infiltrate of basophils, lymphocytes, and eosinophils. These may respond completely to a brief burst of corticosteroid and may be relatively refractory to antihistamines. At present, glucocorticosteroids and antihistamines are gold standard treatments for allergic diseases as a result of their anti-inflammatory and symptom relief properties respectively. Non-sedating H1-antihistamines and topical corticosteroids can well control the symptoms. Inhaled corticosteroids are highly effective at suppressing airway inflammation through inhibiting the expression of cytokines, chemokines and adhesion molecules [14]. Since they are not effective on all patients and may cause numerous side effects, there is a strong recommendation against the long-term use of corticosteroids outside specialist clinics if it can be avoided.

Other drugs

There are many scientific studies published on the treatment of allergic diseases with immune-modulating drugs including cyclosporine, dapsone, colchicine and others. Cyclosporine A has a moderate, direct effect on mast cell mediator release. However these drugs cannot be recommended as standard treatment due to a high incidence of adverse effects such as hypertension, kidney disease, blood dyscrasias, retinopathies, and hyperlipidemia [15]. Short- and long-acting β2-adrenoceptor agonists are now the main treatment of asthma. After binding to the β2-adrenoceptor, adenylate cyclase is stimulated by the signal-transducing G protein to increase production of cAMP, thereby activating protein kinase A to mediate smooth-muscle relaxation. It is the most effective bronchodilators currently available for the rapid relief of asthma symptoms [16]. In the case of rhinitis,α-adrenoceptor agonists are used to relieve nasal congestion. Since some allergic diseases frequently coexist in the same patients, combination therapy is advisable to improve the health of the patients.

Allergen-specific Immunotherapy (AIT)

The use of AIT was initiated almost a century ago. The basic principle of AIT is to induce allergen tolerance through administering repeated, increased doses of allergenic molecules, in order to activate tolerance-inducing cells and mediators, and prevent new allergen sensitivities. With AIT, allergen extracts are presented to the immune system either subcutaneously (SCIT) or sublingually (SLIT) [17]. AIT is the only treatment that has a disease-modifying effect and leads to decreased requirements for anti-inflammatory medications [18,19]. Allergen immunotherapy can induce long term allergen desensitization, which offers the possibility of a cure for allergic diseases [20]. Although efficacious in selected individuals, the currently licensed allergen extracts retain the problems of IgE-mediated side effects and limited efficacy. Several approaches to reduce allergenicity have been explored as below, some with evidence of clinical evaluation.

Allergen extract or recombinant allergens

Allergen vaccines have long been manufactured from the extraction of natural allergens such as mite cultures and pollen grains. So far, all registered products on the market are based on native or chemically modified allergen extracts [21]. However, administration of these allergens can sometimes cause severe, often life-threatening allergic responses. The success of AIT depends on the quality and composition of appropriate allergenic source. Earlier studies mainly focused on the chemical modifications of allergens. Over the last 25 years, genetic engineering techniques are now replacing the chemical procedures for the reconstitution of allergen extracts. A study that used recombinant major birch pollen allergen rBet v 1 to treat birch pollen allergic patients was compared to the treatment with purified natural Bet v 1 extract, and demonstrated that recombinant allergen was as effective as the purified natural allergen [22]. In another trial, mixture of five recombinant grass pollen allergens was proved effective in reducing symptoms and medication usage [23]. In addition, recombinant allergens have also been successfully used in diagnostic tests. Recombinant allergens contain precisely defined concentrations of the active ingredient and can be formulated in a standardized manner [23]. Currently, the concept of allergen standardization during manufacturing process is one of the cornerstones of AIT. Many countries have set up requirements to guarantee the safety and efficacy of allergen product [17,24].

The development of hypoallergenic derivatives of recombinant allergens is one of the strategies to improve the safety of AIT, aimed at inducing T cell tolerance and generating IgG4 blocking antibodies [21]. Recombinant derivatives of allergens such as site-directed mutants and oligomers (dimers, trimers) are piloted to replace allergen extracts. For example, purified mCyp c 1, the major allergenic protein, parvalbumin, with two functional Ca^{2+}-binding sites mutated is developed for fish allergy, and is now being tested in a first-in-man phase I/IIa two-center, randomized double-blind placebo-controlled clinical trial [25]. Such modified, conjugated allergens or multiple allergens over single allergen immunotherapy have been shown to be promising in preclinical characterization [26].

T/B-cell-epitope-based synthetic peptides

The development of short peptides representing T-cell epitopes is another approach to improve safety of AIT, which has been under development and clinical evaluation for two decades [27]. Since T-cell epitopes represent linear amino acid sequences, and B-cell epitopes are in their intact three-dimensional conformational structure [28]. Therefore, allergens are carefully designed as short synthetic peptides that preserve T cell reactivity which can induce immune tolerance,

but too small to bind IgE or induce blocking antibodies. They lack inflammatory cell stimulatory capacity, and thus attenuate or avoid IgE-mediated allergic responses [29]. In a study, subcutaneous injection with three T-cell-epitope-based peptides of the major bee venom allergen PLA2 has been proved effective [8]. T-cell-epitope-based peptides therapies were first investigated for cat allergy treatment using two long 27 amino acids from the two chains of Fel d 1, the major cat allergen. So far, second generation is designated as synthetic peptide immuno-regulatory epitopes (SPIRE) [30]. The first product of SPIRE, CAT-PAD, which derived from Fel d 1 (11–17 amino acids in length), is currently being investigated in phase- III trials [17]. A short course of Cat-PAD improves the ocular and nasal components of rhinoconjunctivitis symptoms in subjects with cat allergy, with the treatment effect persisting 2 years after the start of treatment [31]. Sustained efficacy with few adverse events is being reported for cat, house dust mite and grass pollen allergy after only a short course of treatment. However, in some cases, residual tertiary structure still leads to crosslinking of IgE. Further clinical trials are needed to optimize the short peptides for both safety and efficacy. T-cell-epitope-based peptides therapy is promising a safe and effective new class of AIT, enabling wider application for more severe allergic diseases.

In addition, when B cells present low concentrations of antigen to T cells, high IL-4 but very little IFN-γ is produced. High antigen doses presented by monocytes and macrophages leads to high IFN-γ but low IL-4 synthesis, resulting in lower IgE and higher IgG production. These allergen-specific IgG will compete with IgE for allergen binding to prevent allergen-induced degranulation. Synthetic peptides with three-dimensional structure of an allergen has the potential to induce the production of blocking IgG [8]. A more recent alternative strategy is the use of B-cell-epitope-based peptides not representing dominant IgE epitopes, conjugated to an immunogenic carrier protein, thus aiming to induce blocking IgG4 antibodies without activation of allergen-specific T cells nor the risk of IgE-mediated side effects [32]. BM32 is such a recombinant fusion protein of the PreS domain of HBV fused to non-allergenic peptides representing B cell epitopes from the four major timothy grass pollen allergens. The preS domain of HBV both functions as a non-allergenic carrier protein which will induce T cell activation for IgG antibody production and might even induce antiviral antibodies [21]. This vaccine has been developed and has already been evaluated in phase I/IIa clinical studies.

Allergen in combination with toll-like receptors agonists

Toll-like receptors (TLRs) are innate immune receptors, which respond to specific molecular patterns from pathogens and stimulate the immune system to induce Th1 and reduce Th2 responses. There have been a variety of strategies using TLR agonists as a therapy for allergic diseases. They are mainly used as an adjuvant in AIT to improve traditional SCIT. Endotoxins are agonists for TLR4 receptors. Pollinex Quattro is consisting of tyrosine-absorbed specific pollen extract and enhanced with TLR4 agonist monophosphoryl lipid A as an adjuvant. Therapeutic trials of Pollinex Quattro have been conducted in patients with grass and tree pollen allergy. It induces a significant Th1 immune response, characterized by an increase of allergen-specific IgG antibody levels and reduction of seasonal increase in IgE levels [33]. CpG-containing immunostimulatory sequences (ISSs), which signal through TLR9, are also being developed as a therapy for allergy and have proven to be well tolerated in humans. The molecular basis by which CpG-DNA elicits immunostimulatory activity remains to be elucidated [34]. Covalently bonding an ISS with an allergen, such as ragweed antigen (Amb a 1), has been proved efficacious in control of nasal symptoms of patients with allergic rhinitis. In addition, it leads to a shift of antibody production from IgE to blocking IgG antibodies. Another therapeutic option involves packaging CpG ISS into virus-like particles (VLPs) to protect them against proteases and improve uptake by APCs. A large phase IIb study is now underway [35]. Administration of house dust mite (HDM) allergen extract plus CpG inserted into VLPs markedly increased HDM-specific IgG and IgM levels within 30 days of treatment. TLR agonists either alone or in combination with allergen are novel and promising targets for allergen immunotherapy in the future [35].

Allergen-encoding DNA vaccination

Allergen-encoding plasmid DNA provides a novel type of immunotherapy for allergic diseases [36]. Lastly, a study introduces the so-called LAMP-vax™ DNA vaccines. It uses an unaltered recombinant allergen coupled to an adjuvant protein, the Lysosomal-associated membrane protein (LAMP). Upon immunization, APCs take up the DNA and produce the encoded allergen protein sequence inside the cell as part of the fusion protein with LAMP, directing the fusion protein into lysosome and MHC-II pathway. As a result, the immune system is primarily activated through the MHC-II/$CD4^+$ helper T cell pathway [21]. A phase I safety and tolerability study has just been completed with a CryJ2-DNA-LAMP, a fusion of LAMP and the Japanese red cedar allergen CryJ2. A similar vaccine for peanut allergy, ARA-LAMP-vax is now under preclinical development [21]. Effects of DNA vaccines include the stimulation of Th1 cells and the induction of a balance between Th1 and Th2 cytokines. However, systemic production of allergen by transfected cells also have unwanted side effects. One possibility to reduce allergenicity would be the creation of hypoallergenic DNA vaccines that encodes hypoallergenic allergen derivatives. Furthermore, the development of DNA replicon-based and multiple DNA vaccines enable a lower vaccine dose with antiallergic efficacy of multiple allergens [37].

The DNA vaccine revolution has opened up a new era for protective and therapeutic treatments of allergy. In addition to injection of plasmid DNA, the oral delivery of chitosan–DNA nanoparticles, has been proved to be effective in modulating murine anaphylactic responses [38]. By using new routes for administration such as epidermal immunotherapy(EPIT) and intralymphatic immunotherapy(ILIT), as well as combinations with new adjuvants (Aluminum hydroxide, Lipid-Based Vesicles), it is possible to achieve stronger stimulation of the immune system at unchanged doses or higher doses can be sequentially administered without risk of severe anaphylactic reactions [30].

Non-specific Therapeutic Manipulation of Allergy

Anti-IgE therapy

As an effective diagnostic biomarker of allergy, IgE is capable of switching on allergic reactions within minutes. Thus, IgE has long been considered an ideal target for anti-allergy treatment. Omalizumab is a humanized monoclonal anti-IgE antibody that targets the Cε3 domain of IgE. It can reduce circulating free IgE level and interrupts IgE binding to FcεRI receptors on mast cells or basophils, thus inhibits the subsequent allergic responses. First approved in 2003, Omalizumab has now been used for treating severe allergic asthma in many countries. Clinical observations has also proved its effectiveness in rhinitis, atopic dermatitis, allergic urticaria, and anaphylaxis [39]. Once Omalizumab has bound to IgE, it forms small soluble complexes that are then cleared from the reticuloendothelial system [40]. As IgE upregulates FcεRI on the surface of mast cells, the reduction in the amount of free IgE also results in a decrease in the number of IgE receptors and mast cell population. Studies showed that Omalizumab effectively reduced both the early and late asthmatic responses [41]. In addition, Omalizumab has been demonstrated to be able to prevent systemic reactions to allergen immunotherapy [42].

The adverse effects of monoclonal antibodies (mAbs) result from either target or off-target effects. Target effects are specifically associated with blocking or increasing the function of the target molecule. On the other hand, off-target effects can result from the binding of mAbs to target antigen in irrelevant sites [39]. Additionally, mAbs have been reported to induce hypersensitivity, acute anaphylaxis (IgE-mediated), pseudoallergic reactions and cytokine release syndrome. Although Omalizumab has a good safety profile and the adverse reaction commonly includes injection site induration, itching and pain, some cases have been serious and

potentially dangerous. Therefore, people receiving Omalizumab require to be monitored for a period of time after their injections [43]. Since mAbs are characterized by high costs, it is extremely important to have the proper characterization of the 'right patient' with specific diagnostic markers [39]. Studies with Omalizumab have also shed new light on the multifaceted roles of IgE in allergic disease and immune homeostasis, and thus many efforts are still needed to explore new anti-allergic mAbs.

FcεRI as a therapeutic target

The interaction between allergen, IgE and its high affinity receptor (FcεRI) is an initial component of allergic response [44]. To interrupt the binding of IgE to FcεRI or inhibit FcεRI crosslinking is an attractive strategy for therapeutic intervention of allergic diseases. The structure of FcεRI contains an α-chain, a β-chain and a homodimer of γ-chains. FcεRIα comprises two extracellular domains that bind a single IgE, a transmembrane domain that contains a conserved aspartic-acid residue and a short cytoplasmic tail. The β- and γ-chains have no role in ligand binding. Anti-FcεRIα mAb can decrease the severity of allergy by targeting FcεRIα on mast cells and basophils, progressively removing free FcεRI or probably FcεRI/IgE complexes from cells [45]. Theoretically, application of anti-FcεRIα mAb would provide a safe, effective way to suppress all IgE-mediated allergy. However, anti-FcεRIα mAb itself has the potential to trigger FcεRI crosslinking directly and results in anaphylaxis during desensitization process. Although anti-FcεRIα mAb is proved effective in animal models, and has been produced using different approaches from the use of human hybridoma to the phage-display technology, the advantages and safety remain to be concerned and evaluated in humans [45].

Soluble truncated form of the α-chain of FcεRI can be found in human serum [46]. It's characteristic of interacting with the Fc-region of IgE in extracellular matrix. As a free IgE receptor, sFcεRI can form a complex with IgE, and blocks IgE from binding with other FcεRI receptors expressed on cell surface. Meanwhile, sFcεRI reduces free IgE level, and thus holds the potential as a biomarker as well as a therapeutic agent [47]. Compared to antibodies, small molecules like cyclic peptides and small proteins would be a more convenient form to target IgE-FcεRI interaction [48]. Targeted elimination of mast cells and basophils is also a promising strategy for the treatment of allergic disorders. Our reseach team prepared anti-FcεRIα Fab fragment conjugated celastrol-loaded (PEO-block-PPO-block-PEO, Pluronic) micelles. Anti-FcεRIα Fab-conjugated drugs can target FcεRIα and selectively kill mast cells and basophils which express FcεRIα, and suppress the allergic inflammtion in animal models [49].

Inhibitors of mast cells degranulation

Mast cells are important participants of allergic responses, and the regulation of mast cells is therefore of intense interest for the treatment of allergic diseases. Mast cell stabilizer, disodium cromoglicate (DSCG), has been on the market for years, but their adverse effects include potential hepatic and gastrointestinal disorders. Modulating the expression of activation and inhibitory receptors is an important mechanism for regulating mast cells degranulation. For example, FcγRIIB can negatively regulate FcεRI signaling [50]. Fcγ-Fcε fusion protein (GE2) which is designed to inhibit FcεRI signaling by coaggregating FcεRI with the inhibitory receptor FcγRIIB has been shown to inhibit mast cell activation and block cutaneous anaphylaxis [51]. Furthermore, co-ligation of allergen protein with human IgG Fcγ is a concept for new approach to negatively regulate mast-cell degranulation in an allergen-specific manner. A study demonstrates that fusion protein composed of a truncated human IgG Fcγ and the major cat allergen Fel d 1 inhibits human basophil and mast cell degranulation. Such inhibition was associated with altered Syk and ERK signaling [52,53]. Our research test the FcγRIIB-mediated immunomodulating activity of recombinant Fcγ-Der f2 fusion protein in a Der f2-allergic murine model. The recombinant protein is demonstrated to function as an effective immunotherapeutic agent, suggesting that chimeric human Fcγ-allergen proteins could be used in the development of AIT for human allergic diseases [54]. Signaling downstream of the FcεRI is well characterized to involve activation of the phosphatidylinositol 3-OH kinase pathway, the mitogen-activated protein kinase pathway, sphingosine kinases and transcription factors. Regulators of the pathways are required to sustain mast cell homeostasis and are vital for the identification of potential therapeutic targets [55].

Targeting cytokines and cytokine receptors

The inflammatory process of allergy is coordinated by cytokines network. The production of IL-4, IL-5, IL-9, Eotaxin, GM-CSF and IL-13 by allergen-specific Th2 cells contributes to the differentiation of mast cells, as well as the development, survival and recruitment of eosinophils [56]. For example, IL-2 is generally considered as a key factor in Treg cell homeostasis. A study shows that Daclizumab, a humanized mAb that blocks IL-2 receptor alpha chain of activated T cells affects Treg population and function, and improves asthma control in patients with moderate to severe asthma [57,58]. IL-4 is the major factor regulating IgE production by B cells, and promotes Th2 cell differentiation. Several clinical trials have evaluated the efficacy and safety of mAb to IL-4 (Dupilumab, Pascolizumab), which was shown to reduce asthma exacerbations [59]. Since IL-4 interaction with IL-4Rα is a common pathway in many allergies, recombinant soluble IL-4 receptor and IL-4Rα antagonist also effectively inhibit IL-4 signaling [60]. However, due to the high similarities of IL-4 and IL-13 signaling, approaches that only block IL-4 is not sufficient to inhibit the development of allergic diseases in experimental models[61,62]. It may be necessary to block both IL-4 and IL-13 (Lebrikizumab). Drugs that target cytokines of Th2 pattern and the related receptors--Suplatast tosilate (IPD®) are promising agents in the treatment of allergy [63]. IPD inhibits the production of Th2 cytokines, such as IL-4 and IL-5, in T lymphocytes to alleviate allergic inflammation [12]. IL-25 secreted from infiltrating mast cells also plays a crucial role [64]. Anti-IL-25 therapy can reduce the infiltration of inflammatory cells and inhibit expression of local inflammatory cytokines [65]. Antagonists of TNF-α, which have been successfully used in case reports, are recommended currently only to be used in specialized centers as last option (i.e. for delayed pressure urticaria) [9]. Mepolizumab is a fully humanized mAb against IL-5, which is newly approved for severe asthma with an eosinophilic phenotype. It effectively depletes eosinophils numbers in the airway, bone marrow and blood, and reduces asthma exacerbation frequencies [66,67]. Thus, targeting cytokines and cytokine receptors suggest promising possibility of treating allergic diseases.

Conclusion and Future Directions

Despite decades of deeper research insights into the underlying mechanisms involved in allergic diseases, it is disappointing that most of the experimental observations in animal models have not yet been translated into new treatments. As evidenced by the therapeutics discussed above, the field of therapeutic strategies is constantly developing, and numerous new biopharmaceutical products are in clinical trials and may be approved to market in the near future [67]. They are powerful tools to target different effecter molecules at various points in the signaling pathways on different inflammatory cells associated with allergic diseases. Anyhow, continued researches into new well-tolerated and more effective agents for more convenient treatments of allergic diseases are urgently required. As we continue to elucidate allergic diseases and further characterize the signaling pathways and multiple phenotypes of the diseases, it becomes more and more evident that the universal key for favorable outcome is the selection of appropriate drugs for appropriate patient [39]. Our review provides an overview of the current therapeutics and those that are still under research. And we hope to offer an improved understanding of the recommended therapeutic approaches towards allergic diseases, which will contribute to personalized medication, greater patient satisfaction, reduced health care costs, and to drive the exploration of new therapeutic options.

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