Advances in targeted drugs for allergic diseases

Xue-Song Wang[1], Guo-Yan Wang[2], Hong-Bin Song[3], Yong-Hong Lei[4], Hong-Tian Wang[5,6,7]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Binzhou Central Hospital Affiliated to Binzhou Medical College, Binzhou, Shandong 251700, China;
[2]Department of Ophthalmology, First Medical Center, Chinese PLA General Hospital, Beijing 100853, China;
[3]Department of Dermatology, First Medical Center, Chinese PLA General Hospital, Beijing 100853, China;
[4]Department of Hospitalization and Medical Record Management, Hainan Branch, Chinese PLA General Hospital, Sanya, Hainan 517000, China;
[5]Department of Otorhinolaryngology-Head and Neck Surgery, Hainan Branch, Chinese PLA General Hospital, Sanya, Hainan 517000, China;
[6]Department of Allergy, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China;
[7]Department of Otorhinolaryngology-Head and Neck Surgery, First Medical Center, Chinese PLA General Hospital, Beijing 100853, China.

To the Editor: Since the first IgE monoclonal antibody was approved by the Food and Drug Administration in the USA in 2003, at least 14 kinds of targeted drugs are in the clinical application or pre-clinical trials. The two monoclonal antibodies targeting IgE are omalizumab and ligelizumab. Four drugs targeting interleukin 4 (IL-4) or IL-4R are pascolizumab, pitrakinra, altrakincept, and dupilumab. Three monoclonal antibodies targeting IL-5/IL-5R are mepolizumab, reslizumab, and benralizumab. Two monoclonal antibodies targeting IL-13 are lebrikizumab and tralokinumab. The monoclonal antibody targeting thymic stromal lymphopoietin (TSLP) is tezepelumab. Th2 cytokine inhibitor is mesylate. These targeted drugs have achieved good results, but most of them are still in the pre-clinical stage. This article reviews the history, marketing situation, indications, contraindications, efficacy, and safety of these targeted drugs.

IgE can cause an allergic cascade reaction. Such reaction is triggered by augmenting cellular and humoral immune responses that result from IgR's interaction with the high-affinity IgE receptor (FcεRI) on mast cells and basophils as well as bond with the low-affinity IgE receptor (CD23 or FcεRII). Omalizumab is a monoclonal anti-IgE humanized antibody that blocks allergic cascades through combination with the Cε3 domain contained in IgE to prevent the bind of IgE and FcεRI receptors. Omalizumab has already been proved effective in clinical trials to cure allergic asthma, such as moderate-to-severe symptoms among adults, adolescents, and children.[1] When it is used to treat moderate and severe asthma, the density of IgE in plasma is between 30 and 700 U/mL. When it comes to patients with high IgE density, omalizumab fails to work. Besides, this antibody is safe and effective for healing severe refractory atopic dermatitis.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001349

Ligelizumab (QGE031) is a monoclonal anti-IgE humanized antibody or IgG1. Compared with omalizumab, IgG1 has more affinity for the Cε3 domain of IgE. This means that IgG1 can treat patients with a high level of IgE density more effectively for its better restraints of IgE density.[2]

IL-4 is produced by activated T cells, mast cells, basophils, and eosinophils engaging in regulating Th2's reproduction and existence as well as compounding IgE. IL-4 plays an important role in causing atopic diseases including asthma, allergic rhinitis, and tropic dermatitis.

Pascolizumab is a monoclonal anti-IL-4 humanized antibody that can restrain upstream and downstream events related to asthma, including Th2 cell activation and IgE production. Despite good safety and tolerance, pascolizumab does not show the related effect of relieving asthma.[3]

Pitrakinra is a restructured monoclonal anti-IL-4 humanized antibody targeting Th2 allergic inflammation. It can cure allergic asthma by disordering the activities of IL-4 and IL-13 in a competitive manner to constrain the IL-4Rα compound. After injecting or inhaling pitrakinra, patients who suffered from asthma show excellent tolerance as this antibody can relieve the contractile response of allergic airway in an early or late stage. Pitrakinra can also decrease the deterioration of eosinophilic asthma.[4]

Dupilumab is another monoclonal antibody that can block hardly controlled subunit of IL-4R/IL-13Rα asthma. Dupilumab can greatly reduce asthma attacks of patients who suffer from persistent, moderate-to-severe symptoms and improve lung function.[5] Besides, life qualities are improved for adults hit by moderate-to-severe atopic dermatitis as

Xue-Song Wang and Guo-Yan Wang contributed equally to this work.

Correspondence to: Hong-Tian Wang, Department of Otorhinolaryngology-Head and Neck Surgery, First Medical Center, Chinese PLA General Hospital, Beijing 100853, China
E-Mail: wht301@263.net

Chinese Medical Journal 2021;134(16)
Received: 25-05-2020 **Edited by:** Li-Shao Guo

adverse reactions were alleviated without safety concerns. These reactions include site reactions for injection, nasopharyngitis, conjunctivitis, nausea, and headache.

IL-5 is a cytokine produced by activated T cells. This cytokine sends signals through a pathway consisted of JAK-signal transducer and activator of transcription (STAT), Btk, and RAS/RAF-ERK to maintain the existence and function of B cells and eosinophils. IL-5 is a key factor to facilitate the growth, differentiation, recruitment, activation, and survival of eosinophils.

Three monoclonal antibodies targeting IL-5/IL-5R are mepolizumab, reslizumab, and benralizumab.[6] Mepolizumab is a monoclonal IgG1 humanized antibody that can block the bind between natural homodimer IL-5 and IL-5R. Mepolizumab can markedly curb the development of asthma. For patients suffering from severe eosinophilic asthma, Mepolizumab can safely lower the risks of asthma deteriorating with good tolerance. Besides, this antibody is a new method to treat children's hypereosinophilic syndrome safely and effectively.

Reslizumab is a humanized monoclonal IL-5 antibody serving as a maintenance treatment for patients over an 18-year-old hit by severe asthma with an eosinophilic phenotype. For eosinophilic asthma which is hardly controlled by inhaling corticosteroids, injecting Reslizumab into vein helps reduce the frequency of asthma attacks and improve patients' life quality as well as lungs function remarkably. The most common adverse events of reslizumab are asthma deterioration and nasopharyngitis. There are also other adverse events like an oropharyngeal ache, myalgia, tumor, upper respiratory tract infection, and allergic reaction.

Benralizumab is a non-glycosylated and monoclonal humanized antibody targeting at IL-5Rα subunit. By dependent cytotoxic effect mediated by NK cells, the antibody can directly and rapidly induce eosinophils almost worn out. Benralizumab demonstrates an overall good tolerance for the sick who suffered from severe or even uncontrolled asthma with high eosinophils. Its most common adverse reactions contain nasopharyngitis, asthma exacerbation, and upper respiratory tract infection.

IL-13 is mainly generated by type II T helper cells and mast cells in an activated phase. Such substances can activate tyrosine kinases (eg, JAK1, JAK3, and Tyk2) via tying IL-13Rα and IL-4Rα. These kinases can facilitate the phosphorylation of tyrosine residues and trigger gene transcription in the nucleus after bonding with IL-4Rα. Eventually, such a bind cause allergic symptoms as the calcium pathway is activated. IL-13, a multifunctional cytokine, stimulates an increase of airway mucosal excreta which leads to more airway mucosal NO and hyperresponsiveness at last. As IL-13 is a regulator of allergic asthma, it will be effective to alleviate patients' clinical symptoms by blocking IL-13. Thus, it is essential to find cytokine inhibitors.

As monoclonal anti-IL-13 antibodies, lebrikizumab and tralokinumab are mainly used to treat allergic diseases, such as asthma and atopic dermatitis.[7] Lebrikizumab can act as an inhibitor by preventing the bind between IL-4Rα and IL-13α1. Such effect is testified by a significant decrease of periostin protein density in Th2 patients' blood. Researches on lebrikizumab antibodies and severe atopic dermatitis are in the IIb stage of clinical practices. It is found that lebrikizumab antibodies effectively improve the eczema area and severity index of atopic dermatitis, while clinical researches of tralokinumab are between II and I stages. These researches find tralokinumab's effectivity to mediate symptoms of moderate-to-severe allergic asthma. However, both antibodies are seldom reported related researches on allergic rhinitis, which means further studies about safety and effectivities are still required.

TSLP is a new IL-7-style cytokine that is mainly expressed by epithelial cells and has a similar structure with IL-7. This cytokine plays an important role in triggering allergic rhinitis, asthma, and atopic dermatitis.[8] When epithelial cells are irritated by allergens, allergic inflammatory responses emerge for higher TSLP expression and more Th2 cytokines. It is stated that the TPSL of allergic rhinitis model mice is highly expressed. It is also found that inhaled allergens can increase patients' dendritic cell levels and TSPL receptors. Such found demonstrates the possibility that TSLP engages in allergic diseases' generation and development.

A notably lower incidence of asthma has been proved by researches about tezepelumab's application. Nevertheless, this antibody does not work well to cure none-Th2 patients. Although tezepelumab's function to relieve moderate-to-severe atopic dermatitis symptoms has been also been proved, more researches are still required for specific effectivity and safety of this clinical IIa stage antibody. And reports on the antibody's function to allergic rhinitis are seldom published, yet some increase expression of tezepelumab is spotted in the research of injecting this antibody to mice with allergic rhinitis. This finding provides a potential target of treatment in clinical trials.

As key helper cells of an allergic reaction, Th2 cells are mainly provoked by IL-4 which can also help B lymphocyte produce IgE antibodies. As a close tie exists between cytokines secreted by Th2 cell subsets and allergic disease's development, it is effective to prevent allergic diseases using medicines to curb T lymphocytes into Th2.

As a new selective Th2 inhibitor, suplatast tosilate can alleviate the airway's inflammatory reaction as it selectively curbs the function of the helper T cell to reduce the generation of IL-4 and IL-5. At present, this inhibitor is adopted in early prevention and treatment of allergic diseases like bronchial asthma, allergic rhinitis, and atopic dermatitis. This inhibitor's function of relieving allergic rhinitis is contributed to curbing cytokine related to Th2. Asthma symptoms can also be eased as suplatast tosilate can restrain the expression of IL-5, an inflammatory medium. Therefore, suplatast tosilate is adopted to prevent children's asthma in autumn.[9] It is also found that atopic dermatitis can be alleviated by eating suplatast tosilate. Only a few patients show some side effects such as disorders of liver or kidneys function in a short time, therefore, suplatast tosilate is somewhat effective and safe for most patients.

Therefore, to select the targeted drugs, clinicians need to make a careful judgment based on medical history, detailed

laboratory examination, and other data to make sure which patients will benefit from the use of these drugs, which patients will have slow or no effect after use, and which targeted drugs and their doses.

Funding

This work was supported by grants from the Major Project of Hainan Province (No. ZDKJ2016008), the Key Project of Social Development in Hainan Province and Matching Fund from Sanya City of Hainan Province (No. ZDYF2016127), and the National Natural Science Foundation of China (Nos. 81371074, 81670901).

Conflicts of interest

None.

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How to cite this article: Wang XS, Wang GY, Song HB, Lei YH, Wang HT. Advances in targeted drugs for allergic diseases. Chin Med J 2021;134:2006–2008. doi: 10.1097/CM9.0000000000001349