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Treatment methods for children with severe asthma in and abroad

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Abstract. Asthma is one of the common chronic diseases in children, and so far there is no cure for asthma. Asthma sufferers are estimated to be more than 300 million people worldwide, and the number of asthma treatments is growing every year. In recent years, thanks to advances in therapeutic medicines, asthma symptoms can now be successfully controlled with inhaled corticosteroids and, if necessary, in combination with bronchodilators. However, even with maximum use of these drugs, the effect may be insufficient, and there are still some patients with refractory asthma that are not adequately controlled with general treatment. Drugs called biologics may become a drug that works well for previously poorly treated asthma and is recently available in children with severe asthma. Three biologics are currently available for use in children: omalizumab, mepolizumab (6 years and older), and dupilumab (12 years and older). However, there is still a lack of clinical research evidence for the specific clinical improvement rate. Therefore, in this study, this paper conducted a literature review on the latest clinical trials of biological agents at home and abroad, summarized the clinical trials of common biological agents, and introduced the latest treatment methods. The differences and deficiencies between each other achieve the effect of enhancing the prevention and cognition of asthma.

Keywords: Asthma, childhood asthma, latest treatments, literature review, statistical methods.

1. Introduction

Bronchial asthma is one of the most common chronic diseases of our time, and this disease does not heal with age. Bronchial asthma (asthma) is characterized by chronic and recurrent inflammation of the bronchi (airways), which are the passages of air, causing the bronchi to narrow. In Japan, 5-7% of children and 3-5% of adults are said to have asthma. Childhood asthma is more common in boys and is almost always caused by allergies.

Worldwide, there are estimated to be more than 300 million people with asthma, and the number is increasing every year, and it is predicted that by 2025, there will be about 400 million people with asthma [1]. Nearly 250,000 people die from asthma every year, and so far there is no cure for asthma, but with proper medication and self-management, a life indistinguishable from a healthy person can be achieved.

Since 2000, the availability of effective anti-asthmatic medications, primarily inhaled corticosteroids, has improved control for many asthmatics. However, even in modern times when anti-asthma drugs are widely used, there are still many cases of asthma, even with adequate drugs, the symptoms cannot be controlled, that is, cases of refractory asthma. According to the Japanese Guidelines for Asthma

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Prevention and Management 2018 (The Japanese Society of Allergy, 2018), refractory asthma is defined as asthma that cannot be stabilized even with high-dose inhaled corticosteroids and various anti-asthmatic drugs. Refers to asthma that frequently (continuously or frequently) requires the use of oral steroids. This group of patients is a socially concerned group of asthma patients, not only because of the high frequency of emergency room visits and hospitalizations for attacks but also because of the significant impact on healthcare costs.

Early-onset allergic asthma often occurs in children. "Early onset" refers to the first occurrence of asthma before the age of 12, but in fact, nearly 95% of children with asthma developed before the age of 6. Among them, there are many reasons for children's asthma attacks, one of the most common reasons is caused by air allergens, data show that more than 90% of children with asthma have the possibility of immunoglobulin E-mediated aeroallergen allergy. Fortunately, they are also preventable.

In addition, there are two major predictors of childhood asthma, intrinsic genetic and extrinsic environmental risk factors. Intrinsic factors refer to gender, race, atopic venereal diseases of individuals and parents, various gene polymorphisms discovered by recent studies, and so on. External influences mainly lead to changes in the body through external factors, such as environmental tobacco smoke, air pollution, and early exposure to microorganisms and air allergens, all of which can lead to the onset of asthma [2].

Immediately afterward, in recent years, comorbidity has been increasingly proven to have many effects on childhood asthma, and it is a negative effect. Comorbidities may cause asthma to become uncontrolled, exacerbate the clinical manifestations of the disease, and have received extensive attention. For example, in Japan, allergic rhinitis is one of the important causes of asthma exacerbation in children under 12 years old [2]. A series of studies by Boulay et al. have shown that whether children's asthma is well controlled is related to allergic rhinitis, and the more severe the rhinitis, the longer the duration will lead to worsening asthma and difficulty in getting good relief [3]. Therefore, in conclusion, asthma comorbidity is selected as an important consideration in comprehensive allergy treatment strategy at this stage.

Therefore, we turned our attention to the children group and aimed at continuous treatment of asthma. Given the lack of clinical research evidence for the specific clinical improvement rate and the differences between domestic and foreign studies, this paper reviewed the relevant literature and reviewed diseases such as childhood asthma. Based on the latest domestic and foreign consensus, strengthen the awareness of asthma awareness. Prevention and cognition lay the foundation for future large-sample clinical diagnosis, treatment, and prognostic studies.

2. Treatment of childhood asthma

Next, I will introduce some common treatment methods for childhood asthma as well as some special treatment methods.

2.1. Method one: omalizumab

Asthma in children is a common allergic disease. Omalizumab is an intuitive, steroid-sparing biologic therapy for severe childhood allergic asthma by blocking allergen-specific IgE and its high dose. According to the instructions of the Japanese Ministry of Health, Labor, and Welfare, omalizumab, an anti-IgE antibody therapy, has passed the post-marketing monitoring research, so it is officially approved to be listed in Japan. In addition, this drug was added to the Japanese Children's Asthma Guidelines before 2017, and it is specially used for children's asthma disease. And there are also studies showing that omalizumab treatment can effectively and safely control severe allergic asthma in children, and has other positive effects, reducing medical costs and corticosteroid use, ICS, and OCS in the global pediatric population. Among them, more than 20% of children can stop taking OCS completely [2].

In the context of no clinical studies of omalizumab in children with asthma in Japan, Hiroshi Odajima and Motohiro Ebisawa (2015) conducted a clinical trial in children who all had in common severe allergic asthma. To examine whether the efficacy of omalizumab is also effective in children with severe allergic asthma in Japan, free IgE suppression and safety are also the focus of the study. The observed

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index is the serum-free IgE level. If omalizumab can reduce this index to less than 25 ng/ml, it is considered that omalizumab can inhibit the disease. A multicentre, non-controlled, open-label study was conducted on 38 Japanese children under the age of 15 years. These patients had experienced inhaled corticosteroids, but severe allergic asthma remained uncontrolled. Results showed that omalizumab reduced free IgE levels below target suppression levels in Japanese children with severe allergic asthma, thereby positively impacting clinical trials. The geometric mean serum-free IgE level at 24 weeks was 16 ng/ml, below the expected 25 ng/mL. In the test results, compared with the initial period, the total asthma symptom score, daily activity score, and night sleep score were all significantly improved, and the asthma attack rate and the probability of hospitalization due to asthma were also reduced by 69.2% and 78.2% respectively ($p < 0.001$). Nearly one-third of the patients also reduced the dose of any asthma control drugs, indicating that omalizumab can improve the symptoms of asthma in Japanese people, and there is no obvious drug resistance [4].

Subsequently, Sankei Nishima and Masanari Kozawa (2019) further considered allergic comorbidities, reflected on the previous clinical trials of omalizumab, and introduced in detail the changes of omalizumab in asthma disease, the prevention of allergic asthma in children, the safety of pregnant women, The efficacy of allergic rhinitis and its impact on the development of food allergy have been studied with some positive results. For example, omalizumab can interrupt airway remodeling, and data from clinical trials in allergic rhinitis can show that the benefit of treatment is increasing. In addition, omalizumab is an effective adjunct to oral immunotherapy (OIT), which accelerates the course of treatment and limits the adverse reactions of treatment. However, whether long-term use of omalizumab is sustainable in improving disease and the future role of omalizumab in children with allergic comorbidities is still an area of research that can continue to develop [2].

2.2. Method two: mepolizumab

In some patients, symptoms were not well controlled despite treatment with omalizumab. As stated in the European Respiratory Society/American Thoracic Society guidelines, if symptoms do not improve within 4 months of treatment with omalizumab, there is little point in continuing the drug.

Kenneth R Chapman and Frank C Albers (2019) evaluated these two agents to see whether asthma control improved in patients with severe eosinophilic asthma who switched to mepolizumab. Patients eligible to participate in the evaluation study were to discontinue omalizumab and switch to an unchanged dose of mepolizumab 100 mg subcutaneously every 4 weeks for more than 30 weeks. The results showed that patients in a state suboptimally controlled with omalizumab effectively improved asthma control after switching from omalizumab to mepolizumab and experienced statistically significant improvements in quality of life and asthma exacerbations Significance and clinical significance were improved, and the test results did not observe the tolerance problem of mepolizumab, which provided practical ideas for clinicians to treat patients with severe eosinophilic asthma [5].

However, the pharmacokinetics and pharmacodynamics of mepolizumab are still very ambiguous, especially in children under 12 years of age with severe eosinophilic asthma. Atul Gupta and Isabelle Pouliquen (2019) characterized mepolizumab and studied up to 12 weeks of active treatment in two groups based on the children's baseline body weight. The results showed that mepolizumab SC provided a higher-than-expected drug exposure rate in pediatric patients, which may be due to the bioavailability of mepolizumab SC in children being higher than that in adults, which was twice the adult level. The treatment effect is also like that of adults, and there is also a tendency to improve asthma control compared with the beginning, and no obvious side effects have been found, which is relatively safe. Although dosing improvements are still needed, based on the broad therapeutic index of mepolizumab, the 40 and 100 mg SC dosing regimens are considered appropriate for children under 12 years of age with severe eosinophilic asthma [6].

For similar reasons to the trials above, data on the treatment of eosinophilic phenotypes in children are too scarce and the molecular mechanisms leading to exacerbations are unclear, Daniel J Jackson and Leonard B Bacharier (2022) compared guideline-based care alone, studied whether adding mepolizumab over 52 weeks reduced asthma exacerbations. 390 adolescents were randomly assigned to

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mepolizumab (n = 146) or placebo (n = 144) and included in the intention-to-treat analysis. During the 5-study period, the mean number of asthma exacerbations was 0.96 in the mepolizumab group and 1.30 in the placebo group. Treatment-emergent adverse events occurred in 30% of subjects in the mepolizumab group, a rate much greater than that in the placebo group, but phenotype-directed therapy with mepolizumab still reduced asthma exacerbations [7].

2.3. Method three: benralizumab

In addition to mepolizumab, benralizumab is also a good drug. Corrado Pelaia and Claudia Crimi (2021) investigated whether shifting the drug to bevacizumab led to better outcomes when initial treatment with omalizumab was suboptimal. They found 20 patients with severe eosinophilic asthma allergies who had been followed for at least a year, and all of them had one characteristic in common: omalizumab would not help their treatment. The changes in final values of lung function and blood eosinophils were evaluated by whether symptoms were controlled after the use of benralizumab, and brought positive results. Compared with the previous omalizumab treatment, after more than 1 year of benralizumab treatment, the patient's asthma was well controlled. There were changes in exacerbation rate, asthma control test score, and blood eosinophil count, among others.

In addition, there was an unexpected finding that sinus-nasal outcome test scores at the end of omalizumab treatment decreased significantly after benralizumab treatment. This result also suggests that a pharmacological switch from omalizumab to benralizumab may be a valuable therapeutic approach for allergic patients with severe eosinophilic asthma in the future. However, there is also a pity that benralizumab cannot be fully controlled in anti-IgE treatment [8].

However, the safety and efficacy of benralizumab long-term treatment beyond 3 years are unknown. In previous studies, patients with severe asthma who completed the long-term benralizumab trial entered the safety extension study BORA, and benerizumab has demonstrated safety and efficacy. William W Busse and Eugene R Bleecker (2021) asked patients already on treatment to continue their regimen in BORA, while placebo patients were rerandomized 1:1 to benralizumab. Also, trial outcomes for adolescents at 2 and 3 years of BORA treatment are reported. Larger changes in lung function were found in adolescents at week 8, more pronounced for patients with a BEC greater than 300/μL, but due to the small number of patients in this trial, the differences between patients were greater. However, long-term use of benralizumab by teenagers will not cause drug resistance, and stable efficacy and safety will be maintained during treatment [9].

2.4. Method four: dupilumab

Another drug, the monoclonal antibody dupilumab, may also be used in children with moderate-to-severe asthma, especially those who are not well controlled with standard treatment. Leonard B Bacharier and Jorge F Maspero (2021) A phase 3 randomized, double-blind, placebo-controlled trial over 50 weeks in more than 400 children under 12 years of age with moderate to severe asthma. The method was to use dupilumab injection according to body weight, or a matching placebo injection every 2 weeks. The results confirmed that among patients with the type 2 inflammatory phenotype, the annualized rate of severe asthma exacerbations was more than double that of the placebo group compared with the dupilumab group. It shows that dupilumab can improve asthma control more than a placebo ($P<0.001$) [10].

Transient increases in blood eosinophil counts were observed in dupilumab clinical trials. So, Michael E Wechsler and Amy D Klion performed an extensive post hoc analysis of more than 6600 patients recently enrolled in the dupilumab trial, assessing absolute blood eosinophil counts at baseline and throughout treatment. The results demonstrated that although dupilumab-treated asthmatic patients had a transient increase in mean eosinophil count, it did not affect the efficacy and few clinical side effects occurred. Therefore, physicians need to make judgments based on the patient's previous medical history and baseline eosinophil count and remain vigilant for symptoms of eosinophilia [11].

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2.5. The rest of the methods

China has a system that is different from Western medicine. Yang Yafeng and Wang Xiaoyan (2021) used TCM ideas to treat children with asthma and used observation acupoint catgut embedding combined with western medicine fluticasone propionate aerosol treatment. The purpose is to improve chronic persistent bronchial asthma in children with lung qi deficiency, spleen, and kidney yang deficiency, and to observe the effect of this method on lung function and serum IgA. More than 100 children with asthma were randomly divided into an observation group and a control group. These patients all had chronic persistent bronchial diseases, and each group received 3-month treatment. The control group was treated with western medicine fluticasone propionate aerosol twice a day. On the other hand, based on the original treatment of the control group, the observation group received catgut embedding at 4 specific acupoints every half a month. The clinical efficacy was evaluated by comparing the symptoms of the two groups before and after treatment. The results prove that the combination of traditional Chinese and western medicine can improve lung function such as lung qi deficiency, symptoms of traditional Chinese medicine, and serum IgA and IgE levels, and the curative effect is better than that of fluticasone propionate aerosol alone. [12].

Nebulized MgSO4 is also often used in severe asthma exacerbations, but clinical data on this inhaler in Thailand are too scarce. Siriporn Wongwaree and Tassalapa Daengsuwan recruited more than 30 children ranging from 2 to 15 years old to compare the efficacy and safety of aerosol inhalation of MgSO4 with ipratropium bromide or fenoterol in moderate to severe asthma attacks. Among them, the patients were subjected to a one-to-one controlled test. Although the number of patients in the test was too small, the results proved the study was not bad. It confirmed that in children with acute and moderate asthma in Thailand, no matter whether inhalation of MgSO4 or other. These drugs have good clinical response and safety [13].

3. Conclusion

The results of clinical trials of omalizumab, mepolizumab, benralizumab, and dupiliumab in children prove that these biological agents have obvious curative effects and can effectively relieve severe asthma in children. This also hides the possibility that omalizumab may gradually be replaced by other biologics, but due to uneven price levels and concerns about side effects, whether more biologics can be used for patients in the future still needs to be considered. In addition, some studies on comorbidities are still in a rather ambiguous stage, because we already know that childhood asthma will be accompanied by diseases such as allergic rhinitis, and the various origins between these diseases and asthma need to be clarified in the future. In addition to the commonly used biological agents, some other treatments also hope to conduct more clinical trials to try some new methods to combat childhood asthma, but there have not been many new studies in recent years, and there is not enough new research. Aiming at the lack of clinical trials for children with asthma, this article collects the trials and results of some drug treatment methods at home and abroad, hoping to play a certain role in medical treatment.

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