Review

The treatment of severe uncontrolled asthma using biologics

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Abstract: The numbers of deaths due to asthma have decreased because of the development of inhaled corticosteroid (ICS) treatment. However, about 5% of patients with asthma are still difficult to control with ICS treatment. In severe uncontrolled asthma, the balance between type 2 inflammation and non-type 2 inflammation is assumed to be different. Asthma can be said to be a heterogeneous disease; however, several biologics have recently been developed for use in severe uncontrolled asthma. Omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab, targeting type 2 inflammation, have been approved for use worldwide. Severe uncontrolled asthma is heterogeneous, and it is becoming necessary to classify phenotype and endotype for individual patients to determine treatment options. This review will explain treatment options for severe uncontrolled asthma, with a focus on biologics.

1. Introduction

Asthma is a chronic respiratory disease characterized by inflammation of the respiratory tract, increased airway hypersensitivity, and reversible airway obstruction, affecting patients of all ages [1]. There are various types of patients, ranging from patients with mild symptoms to those whose treatment is difficult to control, and it affects their quality of life.

Although asthma can be controlled by standard therapy with a combination of inhaled corticosteroid and long-acting β2-stimulant (ICS/LABA) treatment, approximately 3–10% of asthma patients are estimated to suffer from severe asthma [2–4]. They account for more than 50% of all

asthma medical expenses, and new treatments still need to be developed.

Generally, asthma was thought to be based on the involvement of Th2 cells and eosinophilic airway inflammation. However, recently, the presence of non-eosinophilic asthma, which is not associated with a predisposition to allergies and has little eosinophilic inflammation of the respiratory tract, has become prevalent.

To classify simply, asthma is divided into two main categories: type 2 asthma and non-type 2 asthma [5]. Recently, it has been classified by phenotype and endotype based on clinical features, laboratory findings, and genetic background [6–13]. For example, it is classified into allergic eosinophilic asthma, non-allergic eosinophilic asthma, and non-eosinophilic (neutrophilic) asthma.

When making a plan for treatment, it is easy to understand that the treatment method is determined by phenotype and endotype. Not only that, classified by phenotype and endotype seems easy to do research on future therapeutic drugs. Recent studies of severe asthma have shown that the patients are not atopic, and eosinophilia and Th2-cytokines are not characteristic in some cases. In severe asthma, the balance between type 2 inflammation and non-type 2 inflammation is assumed to be different.

In this review, we will summarize the therapeutic options for severe asthma and propose a phenotype-endotype-based treatment algorithm for patients with severe and difficult-to-treat asthma.

2. Basic pathology in asthma

Cytokine-mediated immunity plays a dominant role in the pathogenesis of asthma.

Dendritic cells take up allergens, present antigens to Th0 (naïve T) cells, and differentiate into Th2 cells. IL-5 produced by Th2 cells is a strong eosinophil activator. IL-4 induces IgE production from B cells, and IL-13 is also involved in airway remodeling. In addition to Th2 cells, ILC2 (type 2 natural lymphocytes) cells are activated by IL-25 and IL-33 produced from epithelial tract cells after infection and allergen exposure. They also produce large amounts of IL-5 and IL-13. In short, IL-5 and IL-13 are secreted from both Th2 and ILC2 cells. Inflammation caused by Th2 and ILC2 cells is called type 2 inflammation (Figure 1).
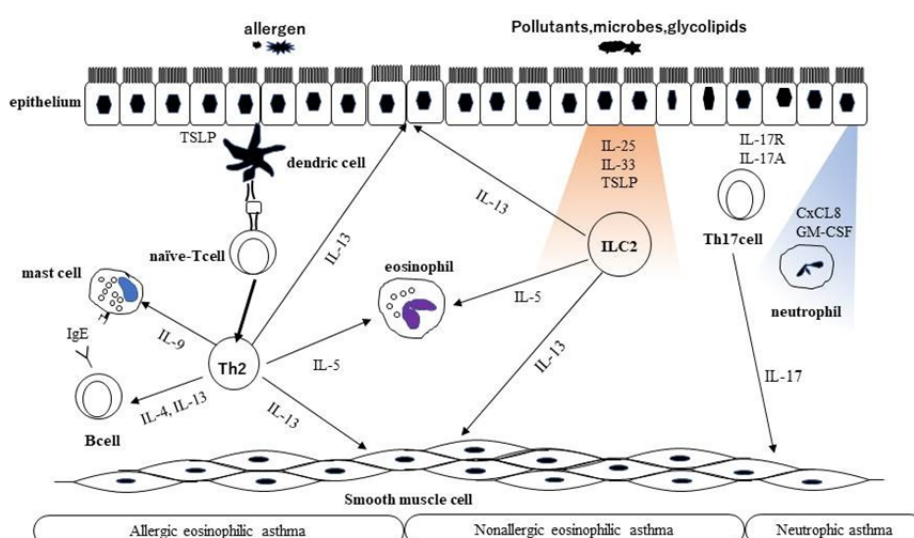
Figure 1. Asthma pathology.

On the other hand, the non-type 2 inflammatory reaction is assumed to involve IL-17 that acts on airway epithelial cells, which induces the production of IL-8 and G-CSF, which induce neutrophil migration and activation. IL-17 has been reported to correlate with neutrophil count and asthma severity [14].

In addition to type 2 therapeutics, non-type 2 inflammation, which is similar to chronic obstructive pulmonary disease (COPD), is also being investigated. At present, biologics targeting type 2 inflammation have been developed and approved, but no biologics targeting non-type 2 inflammation are currently available. Thus, macrolides and bronchial thermoplasty are options for additional treatment of non-type 2 inflammatory asthma.

3. Definition of severe and difficult-to-treat asthma

The definition of severe asthma has changed in recent years. Recent GINA/NAEPP guidelines define asthma severity based on the level of treatment used to maintain adequate asthma control [1,15,16].

Difficult-to-treat asthma is asthma that is difficult to control, even with high-dose ICS treatment and other multiple asthma medications.

Severe asthma is one of the difficult-to-treat asthmas, which is difficult to control even when a leukotriene receptor antagonist or theophylline is used in addition to high-dose ICS/LABA treatment, or systemic glucocorticoid treatment is needed.

4. Biological drugs

Recent studies have reported that blocking IgE, IL-5, IL-4, IL-13, IL-9, TSLP, and CCR3 may be effective in the treatment of allergic eosinophilic asthma [17–24].

Novel therapeutic strategies with type 2 inflammation-targeted biologics have been developed for severe asthma, with omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab having been approved worldwide.

This section mainly describes currently approved anti-IgE, anti-IL-5, and IL-4 agents.

4.1. Anti-IgE (omalizumab)

Patients with allergic diseases have elevated serum IgE levels that induce rapid release of bioactive substances (degranulation reaction) stored in intracellular granules of mast cells and basophils. Thus, IgE is an important mediator of allergic reactions, like histamine.

Omalizumab is the first recombinant humanized IgG1 monoclonal antibody; it binds to free IgE, interrupting the IgE-mediated asthma inflammatory cascade at an early stage. Omalizumab was the earliest approved monoclonal antibody (mAb) therapy for asthma.

The purpose of its interrupting effect is to prevent mast cell activation and subsequent generation of its inflammatory mediators when IgE is activated by allergens. Thus, omalizumab reduces early- and late-phase asthmatic responses.

Randomized, controlled, clinical trials of omalizumab have been performed. Omalizumab significantly decreases asthma exacerbations and reduces the use of oral corticosteroids (OCSs), the amount of ICSs, and rescue use, and improves respiratory symptoms and quality of life [17,25–27].

Omalizumab is usually administered subcutaneously. Although there are some differences in each country, the administration conditions are basically similar.

Patients' serum total IgE and body weight are measured before the first dose. Omalizumab is administered in addition to the standard defined when the concentration is calculated in terms of dose (when 30 IU/mL or more and 1500 IU/mL or less are satisfied).

Additionally, 16 weeks after the start of omalizumab, doctors comprehensively evaluate the effectiveness of treatment, and it should be continued only in patients who show marked improvements in their asthma.

4.2. Anti-IL-5 (mepolizumab, reslizumab, benralizumab)

Eosinophilic bronchial asthma is characterized by increased eosinophil counts in the airways and peripheral blood, which have been shown to positively correlate with asthma severity [28].

Interleukin 5 (IL-5) is a 13-amino acid protein that forms a 52-kDa homodimer binding to the IL-5 receptors on cell surfaces, a heterodimer composed of α and β subunits. The α subunit is specific for IL-5, and it is expressed on human eosinophil and basophil progenitors in bone marrow, as well as on mature circulating and tissue eosinophils and basophils.

The β subunit is responsible for cell signaling, shared with the granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 3 (IL-3) receptors [29,30]. It plays an important role in promoting growth, differentiation, and maturation of eosinophils in the bone marrow, along with their survival and activation in peripheral tissues.

Regarding the pathogenesis of bronchial asthma, IL-5α produced by type 2 helper T cells (Th2 cells) has been shown to play an important role in the pathogenesis of airway inflammation through proliferation and activation of eosinophils [31].

Thus, it was thought that asthma symptoms could be suppressed by an agent 1) if it binds to human IL-5 with high affinity (mepolizumab and reslizumab), or 2) if the binding of the ligand to the IL-5 receptor complex α-subunit could be inhibited (benralizumab). Both anti-IL-5 monoclonal antibodies (mAbs) (mepolizumab and reslizumab) and anti-IL-5Rα (benralizumab) have been shown to reduce circulating eosinophils and improve asthma control in patients with severe eosinophilic asthma, in particular in patients with elevated eosinophilic blood counts at baseline [32]. They are indicated for patients with a blood eosinophil count of 300 cells/μL or more and repeated acute exacerbations.

4.2.1. Mepolizumab

Mepolizumab was the first anti-IL-5 antibody; it binds to Il-5, inhibiting its interaction with its eosinophil surface receptor.

In 2000, a clinical study of mepolizumab was conducted [33], but because the subjects were not limited to patients with eosinophilic asthma, its effectiveness for asthma treatment was not proven. Later, a large-scale study focusing on eosinophilic asthma proved that it was effective [33].

 Thus, when using mepolizumab, it is important to confirm the blood eosinophil count at ≥300 cells/μL.

Efficacy and safety in an international trial were confirmed in severe asthma patients (increased asthma exacerbations more than once in the past 12 months using high-dose ICS treatment and other

therapeutic agents), including Japanese patients. Mepolizumab was approved in the USA and Europe in 2015.

Mepolizumab is usually administered subcutaneously at a dose of 100 mg every 4 weeks [34,35] to patients whose blood eosinophil count was 300 cells/µL or more in the past 12 months.

In the combined analysis of SIRIUS [36] and MENSA [34], adverse events such as headache (19%), injection site reaction (8%), back pain (5%), and malaise (5%) were observed, but there were no cases of anaphylaxis or death. In the long-term COSMOS study [37], the side effect profile was similar.

4.2.2. Reslizumab

Reslizumab is a high-affinity, humanized anti-interleukin (IL)-5 monoclonal (IgG4/κ) antibody. Reslizumab is also directed against IL-5, the same as mepolizumab, which inhibits activity within the IL-5 signaling pathway by reducing ligand-receptor interactions, and it reduces blood and tissue eosinophils in patients with asthma [38,39].

Reslizumab has two features that are different from mepolizumab: it is used intravenously, and its dose depends on weight 3 mg/kg every 4 weeks. Reslizumab is usually administered intravenously at 3 mg/kg every 4 weeks to patients whose blood eosinophil count is ≥400 cells/µL, and it binds to IL-5 directly, the same as mepolizumab. Reslizumab is not currently approved for use in Japan.

4.2.3. Benralizumab

The IL-5 receptor is a heterodimer of an α chain of the IL-5 receptor and a β chain receptor common to IL-3 and granulocyte macrophage colony-stimulating factor (GM-CSF) receptors. Benralizumab is a fully humanized afucosylated IgG1κ mAb that binds to an epitope on IL-5Rα. It inhibits IL-5 signaling, independently of ligand presence [40]. It also sustains antibody-directed cell-mediated cytotoxicity (ADCC) of eosinophils and basophils, leading to depletion of blood, tissue, and bone marrow eosinophilia [41]. Benralizumab is more likely to suppress eosinophilic inflammation than mepolizumab or reslizumab, because it is said that GM-CSF and IL-3 are related to the infiltration and activation of eosinophils in tissues. In clinical practice, it is highly likely that the target patient group will overlap with the anti-IL-5 antibody (mepolizumab, reslizumab) groups, and it is necessary to examine its proper use. The efficacy and safety of benralizumab for patients with severe asthma were confirmed by several studied [42,43]. And, SK Mathur et al. showed an improvement of lung functions in asthmatic patients treated by benralizumab [44].

Benralizumab is usually administered subcutaneously at 30 mg every 4 weeks for the first 3 doses, and then every 8 weeks to patients whose blood eosinophil count is ≥300 cells/µL.

4.3. Anti-IL-4, 13 (dupilumab)

The Th2 cytokines IL-4 and IL-13 were discovered in the early 1980s, and they play a key role in the pathogenesis of allergic disorders. There are two types of IL-4 receptors, type 1 and type 2 [45–47]. The type 1 receptor is a heterodimer of IL-4Rα and a common γ-chain. When IL-4 binds to IL-4Rα, the γ-chain is recruited, and a signal is transmitted into the cell. IL-4Rα is expressed

in various cells, but the γ-chain is expressed mainly in hematopoietic cells. Therefore, the type 1 receptor is expressed mainly in hematopoietic cells such as T cells and B cells. Type 2 receptors are composed of IL-4Rα and IL-13Rα1. The type 1 receptor transmits only IL-4 signals, whereas the type 2 receptor transmits both IL-4 and IL-13 signals. When IL-4 binds to IL-4Rα, IL-13Rα1 is recruited. On the other hand, when IL-13 binds to IL-13Rα1, IL-4Rα is recruited, and signals are transmitted. Type 2 receptors are expressed on some hematopoietic cells, but they are also expressed mainly on non-hematopoietic cells such as epithelial cells.

Dupilumab is a fully human anti-interleukin-4 receptor α monoclonal antibody that blocks both IL-4 and IL-13 signaling, as mentioned above, because IL-4Rα is a common subunit of IL-13 and IL-4. In Japan, it was approved for atopic dermatitis prior to asthma and has been shown to be effective.

Recently, it also gained approval as add-on treatment for moderate-to-severe asthma in adolescents and adults. Phase II and III randomized, controlled trials demonstrated improvements in asthma exacerbation rates, FEV1, oral glucocorticoid use, and a range of patient-reported outcomes.

IL-4 has been shown to stimulate IgE production from B cells, and IL-13 expression correlates with disease severity and flares [48].

In short, IL-4 plays a major role in Th2 cell proliferation, IgE synthesis, and cytokine production. Additionally, IL-13 has a major role in the pathological features of disease (mucus production, airway hyperresponsiveness, and collagen deposition [49]. Regarding IL-13 regulation, it has been reported that inhibiting IL-4R is more effective than only an IL-13 antibody that controls bronchial asthma [50,51]. Therefore, dupilumab is considered to be an effective treatment when patients have abundant airway secretions. The blood eosinophil count and exhaled nitric oxide concentration (FeNO) are effective biomarkers. The usefulness of FeNO in the therapeutic effect of dupilumab is characteristic, unlike anti-IL-5 drugs. Moreover, after therapy, serum total IgE, periostin, TARC, and eotaxin-3 have been shown to be decreased in humans. The number of blood eosinophils increases transiently after therapy and then returns to baseline. This may indicate that, in order to reduce production of eosinophil-directed chemokines in the local area of lung inflammation, blood eosinophils are not mobilized to the lung temporarily.

Dupilumab is usually administered subcutaneously and is approved for use in atopic dermatitis and asthma in adults. In cases of asthma, for adults and children 12 years of age and older, 600 mg of dupilumab is administered subcutaneously the first time, and then 300 mg is administered subcutaneously every two weeks. Side effects are similar to those of IL-5 antibodies, but eosinophilia is unique to dupilumab.

4.4. IL-33 and TSLP

4.4.1. Anti-IL-33

In addition to the Th2 cells and mast cells, IL-33 stimulates Group 2 innate lymphoid cells (ILC2s) to produce Th2 cytokines [52]. On the other hand, IL-33 stimulates Th2 cells together with antigen to enhance IL-5/IL-13 production, and it is also involved in the development and enhancement of acquired allergy. In other words, IL-33 appears to be an important regulator of both natural and acquired allergies [53]. IL-33 antibody are being tested in severe asthma.

4.4.2.   Anti-TSLP (tezepelumab)

Thymic stromal lymphopoietin (TSLP) promotes Th2 differentiation by dendritic cells. ILC2 cells produce a large amount of IL-5 and IL-13 and play an important role in allergic airway inflammation. TSLP induces steroid resistance of ILC2s and helps activate ILC2 [54]. TSLP secreted from respiratory epithelial cells by viral infection or allergen stimulation (i) acts on dendritic cells to promote Th2 differentiation, (ii) suppresses regulatory T cells (Tregs) that act on lymphocyte inhibition, and (iii) induces steroid resistance of ILC2s. When the effects were investigated, asthma exacerbation was found to be suppressed regardless of the number of eosinophils in the blood, and its effectiveness for neutrophilic asthma is of interest. In ongoing Phase III clinical studies, it is necessary to verify whether TSLP antibodies are actually effective in neutrophilic asthma.

5.   In the treatment of asthma

Currently, ICS treatment is the first choice in global guidelines for bronchial asthma treatment.

Depending on the severity, long-acting β2 stimulants, leukotriene receptor antagonists, theophylline, long-acting anticholinergic drugs, oral steroids, etc. are used. However, there are difficult-to-treat asthma cases that develop exacerbations of asthma even after combination therapy with ICS and other drugs.

Recently, several biologics were examined and have been approved to target T2 airway inflammation in patients with severe asthma. Multiple biologics targeting T2-high asthma are effective in the appropriate groups of severe asthma.

Before using biologics, however, it is important to determine whether there are comorbidities that worsen asthma, or whether low-cost treatments such as LAMA and theophylline have been curative. It is also necessary to confirm adherence and consider the use of antibody drugs if any treatment other than biologics still provides poor results.

6.   Summary of uncontrolled asthma treatment strategy

(1) Review of diagnosis
(2) Confirmation of disease complications other than asthma
(3) Confirmation of drug adherence
(4) Increased ICS doses or additional inexpensive treatments
(5) Categorize strategies by type 2 inflammation
(6) Consider molecular biological preparations if acute exacerbations are repeated even after treatment with type 2 inflammation with a high ICS dose and other inexpensive treatments.
(7) In the case of not type 2, the possibility that anti-TSLP and other biological drugs can be expected is considered, but at present, macrolide treatment and bronchial thermoplasty (BT) are used.

7.   Proper use of molecular biologics (Figure 2)

With regard to the use of molecular biologics, since there is overlap in what is applicable to some cases, treating physicians must select the appropriate drugs. Finally, the characteristics that will

be helpful for selection are described.

(1) The oldest anti-IgE antibody (omalizumab) has been established for about 10 years and has shown long-term safety, and it may be possible to discontinue it after long-term use.

(2) Anti-IL-5 and anti-IL-5α antibodies decrease blood eosinophils, but not omalizumab, and dupilumab not only does not decrease eosinophils, but it also increases them temporarily.

(3) Eosinophil depletion ability is even stronger for IL-5α (benralizumab) than for other IL-5 antibodies.

(4) Anti-IgE antibodies are expected to have long-term effects predicted in a comprehensive assessment after 4 months, but the long-term effects of other molecular biologics are unpredictable at this time.Thus, there are reports that anti-IgE antibodies should be used first when indications overlap.

(5) Maintenance treatment with benralizumab is every 8 weeks, and the burden on patients is light. Dupilumab can be self-injected, but it is given every 2 weeks.

(6) Anti-IL-5 has been established to have long-term safety for about 5 years, but the long-term safety of IL-5α (benralizumab) and dupilumab has been shown for only a few years.

Bousquet et al. proposed that omalizumab should be considered first-line therapy due to its safety as assessed by a large body of real-life data and over a decade of post-marketing surveillance [55]. However, not all patients receiving omalizumab seemed to respond well to treatment. The issue is complicated by the fact that blood eosinophil counts are a selection criterion and a strong predictor of response to treatment with mepolizumab, as largely previous reported, while IgE levels guide treatment selection for the use of omalizumab but are not predictive of response to omalizumab. The EXTRA study has instead shown the potential of fractional exhaled nitric oxide (FeNO), the peripheral blood eosinophil count, and serum periostin as predictors of the treatment effects of omalizumab [56]. The benefit of omalizumab is probably greater in patients who have early-onset allergic asthma and in younger patients [57], whereas anti-IL 5 treatments are more suitable for patients with late-onset asthma.

Regarding anti-IL5 drugs, an indirect drug comparison recently showed that mepolizumab was more effective in reducing exacerbations and in controlling asthma in patients with an eosinophil count ≥400 cells/µL compared to benralizumab and reslizumab. The study also found that benralizumab was more effective in improving lung function than reslizumab in patients with an eosinophil count ≥400 cells/µL [58]. However, when baseline patient characteristics were matched across asthma trials, benralizumab and mepolizumab showed similar efficacy [59].

With respect to comorbidities, there have been some studies. For example, Carpagnano GE et al. suggested the efficacy of mepolizumab in terms of reduction of inflammation and increased control in severe eosinophilic asthma with bronchiectasis [60]. Additionally, Alexander et al. suggested the efficacy of anti-IL5 therapy (mepolizumab/reslizumab) and anti-IgE therapy (omalizumab) in nasal polyps with asthma [61].

In my opinion, when asthma is divided into (i) allergic eosinophilic asthma, (ii) non-allergic eosinophilic asthma, and (iii) non-eosinophilic asthma, in the case of (i), when IgE is in the range of 30–1500 IU/mL, first use omalizumab, and consider continuation or treatment change at the 4-month re-examination. If the effect is insufficient at the re-examination, select an anti-IL-5 or anti-IL-5α agent if the eosinophilia is over 500 cells/µL. If there are not many eosinophils, use dupilumab. If there is prominent atopic dermatitis, use dupilumab from the beginning. In the case of (ii), anti-IL-5 and anti-IL-5α agents are used. Anti-IL-5 antibody is used for EGPA, and anti-IL-5α

antibody is used when eosinophilia affects other organs, such as eosinophilic sinusitis and eosinophilic myocarditis. In the case of (iii), there is no effective molecular target drug yet, so the approach becomes dependent on BT therapy, macrolides, and OCS treatment. If IgE in an asthmatic patient meets the amount for use of omalizumab, use omalizumab first and consider continuation or treatment change at the 4-month re-examination. Select dupilumab if there are prominent secretions. Individual patients have different characteristics, and it is dangerous to judge only by pheno-endotype.
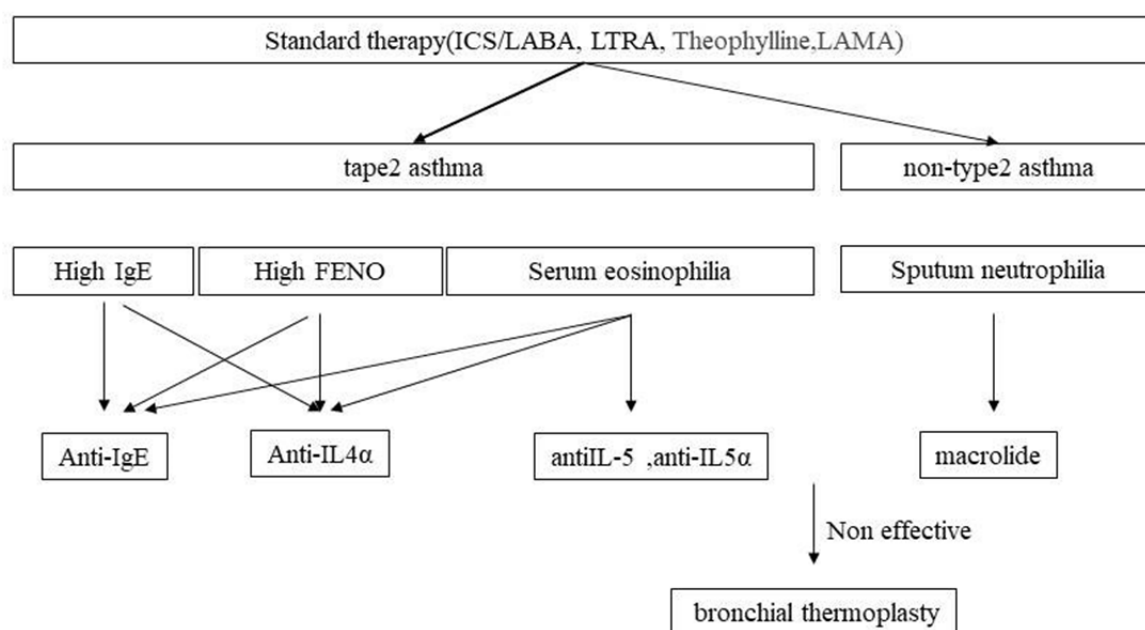
Figure 2. Proper use of molecular biologics.

8. Conclusion

Biologics are effective against severe-uncontrolled asthma, mainly Th2.

Anti-IL-5, anti-IL-4/13, and anti-IgE drugs have been confirmed and approved in large-scale phase III trials. There are other unapproved products, such as anti-IL-13 and TSLP, but the therapeutic agents for Th2-type asthma have evolved and are expected to be useful in the future. With the advent of molecular targeted drugs, stratified therapy based on the phenotype of asthma has begun (Figure 2). Stratified treatment is expected to become more comprehensive with drugs currently being developed and approved in the future.

Future topics include the identification of biomarkers for the treatment of asthma and the development of non-Th2 type therapeutics. In addition, it may be necessary to investigate the use of biologics for long periods of time. To assess the long-term effects including adverse events, asthma patients treated with biologics should be followed for long periods of time.

Conflict of interests

All authors declare no conflicts of interest in this paper.

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