BRONCHIAL ASTHMA: CURRENT TRENDS IN TREATMENT

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Abstract

Asthma is a heterogeneous disease which pathophysiology is still poorly understood. Asthma was traditionally divided into allergic (extrinsic) and non-allergic (intrinsic) types, while patients with allergic type responded better to corticosteroids. Since 2013 the definition of asthma has changed. Recently, better insight into clinical considerations and underlying inflammatory phenotypes has been gained. Defining these phenotypes has already led to more specific clinical trials and, therefore, to more personalized and successfully targeted therapy. For future, much more effort is put in identifying new phenotype-specific biomarkers which could be helpful in stratification of heterogeneous patients with asthma.

Key words: bronchial asthma, asthma phenotypes, asthma therapy

INTRODUCTION

Management of asthma

Bronchial asthma is a heterogeneous respiratory disease characterised by chronic inflammation and airway hyperreactivity (AHR) that affects approximately 300 million people worldwide. Most patients are well-controlled, yet despite the availability of effective conventional therapy, approximately 5–10 % of them suffer from serious asthma condition. These patients respond poorly to a standard therapy because of contribution of multiple factors and underlying pathobiological differences (1, 2).

As a “gold standard” therapy, β_2 -adrenergic agonists and inhaled corticosteroids (ICS) have been used, providing bronchodilating and anti-inflammatory actions, respectively. Combination of these two therapies even enhances the therapeutic effect, while β_2 -adrenergic agonists promote a nuclear translocation of glucocorticoid receptor leading to higher responsiveness to corticosteroids (CS) and CS up-regulate the β_2 -receptors (1–3).

When asthma is not well-controlled despite using CS, the following add-on therapies are recommended (3):

- leukotriene receptor modifiers
- theophylline with sustained release (SR)
- long-acting muscarinic antagonists (LAMA)
- biologics.

Asthma management is being updated every year and described in *Global Initiative for Asthma (GINA)* guidelines (4). Depending on severity and responsiveness to therapy, GINA describes a 5-steps algorithm of asthma management. Although the adverse effects of CS are well-known, due to their high effectiveness they are implicated in each step (ranging

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from low to high dose ICS regimen). In 2019 a fundamental change in management of mild asthma was made. While previously the short-acting β_2 -adrenergic agonists (SABA) treatment alone could be used for mild asthma, the actual guidelines have refused the SABA-alone treatment because of inefficient control of asthma symptoms and suggested low dose ICS formoterol as an initial treatment (4, 5). Recently recommended asthma management according to GINA guidelines 2019 is depicted in the following picture (Figure 1).

Fig. 1 Stepwise approach for adjusting asthma treatment (modified according to Ref. 4).

Although CS have been considered for the most potent anti-inflammatory drugs, there is a significant portion of patients who fail to respond adequately to even high doses and/or suffer from side effects of CS. These individuals with CS-dependant or CS-resistant type of asthma represent considerable management problems as there are few alternative anti-inflammatory treatments available (6).

Asthma subtypes

The concept of asthma has recently changed. Traditionally, asthma patients were divided into those with allergic (extrinsic) asthma and those with non-allergic (intrinsic) asthma (7). Nowadays, asthma has been recognised as an extremely heterogeneous disease in which pathophysiology the T-helper lymphocytes play a crucial role (1, 8). In the **Th2-high asthma** (or type-2 or eosinophilic asthma) an allergen is presented to naive T-cells by dendritic cells, leading to development and activation of Th2 cells producing cytokines (interleukin (IL)-3, IL-4, IL-5, IL-9, and IL-13) in the bronchial submucosa. These cytokines contribute to an allergic airway inflammation that triggers activation and recruitment of immunoglobulin (Ig)E antibody-producing B-lymphocytes, mast cells, basophils, and eosinophils (1, 8). In the **Th2-low asthma** (or non-type-2, non-eosinophilic or neutrophilic asthma) an increased count of Th1-cells producing interferon (IFN) γ and tumour necrosis factor (TNF) α and of Th17-cells producing IL-17 and IL-8 is presented by predominantly neutrophilic inflammation (1, 8, 9). However, besides these two pathways, other mechanisms may participate in the asthma (2).

In patients having similar clinical symptoms (wheeze, breathlessness, chest tightness, cough) differentiation of asthma to phenotypes is of great clinical importance while the phenotypes respond differentially to the therapy. Intensive study of distinct pathophysiologic mechanisms at cellular and molecular levels and differentiation of asthma into phenotypes/endotypes help to find an appropriate and individualized therapy. Better understanding of phenotypes/endotypes of asthma can be implemented in designing clinical trials, i.e. in choosing the right subsets of patients and using the suitable biomarkers to identify them (10).

Treatment of Th2-high or eosinophilic type of asthma

Th2-high or eosinophilic asthma is characterized by increased eosinophil counts in blood and sputum, higher plasma IgE levels, positive skin prick-test, activation of basophils, Th2 cells, natural killers, innate lymphoid cells (ILC2), as well as elevated synthesis of cytokines IL-4, IL-5, and IL-13 (1, 7). Th2-high asthma responds well to CS, however, most available therapeutic strategies are focused on this kind of inflammation (10).

Anti-IgE based therapy

Approximately 70% of patients have an allergic, eosinophilic asthma phenotype, characterized by increased IgE specific to aeroallergens. The first drug approved as an anti-IgE monoclonal antibody was **omalizumab** (approved by the US Food and Drug Administration (FDA): Xolair, 2003; approved by European Medicines Agency (EMA), 2005). Omalizumab binds to C 3 domain of free IgE heavy chain and thereby binds to circulating IgE and down-regulates the high-affinity IgE receptors (FcεRI) on basophils and mastocytes, as well as circulating dendritic cells (11). Nowadays, according to actual GINA, omalizumab is indicated for IgE-mediated moderate-to-severe asthma inadequately responding to conventional therapy.

Cytokines as a target

Targeting IL-5 or IL-5 receptor is used to influence this key mediator for proliferation, activation, and recruitment of eosinophils (12–16). To date, two monoclonal antibodies **mepolizumab** (FDA/EMA: Nucala, 2015) and **reslizumab** (FDA: Cinqair, 2016; EMA: Cinquaero, 2016) have been approved as add-on therapy in refractory eosinophilic asthma. Mepolizumab has been most extensively investigated, showing reduction in exacerbations rate of around 50%. Both of these drugs bind directly to IL-5, while newly developed **benralizumab** (approved by FDA: Fasenra, 2017; EMA: Fasenra, 2018) binds to receptor subunit-α, leading to antibody-dependent cell-mediated cytotoxicity of eosinophils, basophils, as well as eosinophil progenitor cells in bone marrow. This fact makes it theoretically more effective compared to mepolizumab and reslizumab, considering reduced exacerbation rate, improved lung functions, or reduced oral CS use (12–16).

IL-4 and IL-13 were the first mediators identified to drive type-2 inflammation. IL-13 receptor is a complex assembly of both IL-13 and IL-4 receptor subunits. Both cytokines IL-4 and IL-13 are produced by Th2 cells (IL-13 also by ILC2 cells), whereas IL-4 regulates mostly Th2 cell function and IgE synthesis and IL-13 is responsible for mucus production, AHR, and generation of IgE. Currently, many monoclonal antibodies blocking this pathway have been investigated (17–20). Periostin, a downstream IL-13 -induced protein, might be a valuable biomarker showing elevation of IL-13 and airway eosinophilia. **Lebrikizumab**, a monoclonal antibody against IL-13, reduced exacerbation rate and enhanced lung functions particularly in patients with higher periostin level, however, in study Phase III did not demonstrate a consistent benefit after all (21). Drug with similar mechanism of action, **tralokinumab**, has been successfully tested in clinical trials as an add-on therapy for patients with severe uncontrolled asthma who had increased IL-13 titres (Phase 2a). In Phase IIb study, tralokinumab improved symptoms in participants with elevated biomarkers such as DPP-4 and periostin (both indicators of increased IL-13). Despite

lebrikizumab and tralokinumab targeting IL-13 demonstrated some benefits, the studies were unable to identify a population of asthmatics with consistent, clinically meaningful treatment benefit (16–21).

Another treatment strategy is based on IL-4 -receptor blocking which is a common chain for IL-4 and IL-13 receptor, represented by **dupilumab** (18, 19, 22). Blocking both IL-13 and IL-4 seemed to be very promising because of reduced exacerbation rate in patients with a higher eosinophil count in blood, improved FEV₁, and lowered markers typical for Th2 inflammation. Therefore, **dupilumab** has been approved by FDA (Dupixent, 2018) as an add-on therapy for adult and adolescent patients with severe type-2 asthma with increased blood eosinophils and/or raised exhaled nitric oxide measured by FeNO test, inadequately controlled by inhaled high dose CS plus another drug. At the moment, dupilumab is awaiting approval by EMA.

Pitrakinra, recombinant human IL-4 mutein, competitively inhibits IL-4 receptor, thus inhibits both IL-4 and IL-13 pathways. However, in a dry powder inhaled form (Aerovant TM) failed to prove a measurable benefit in clinical trials, probably due to IL-4R polymorphism-dependent effect (23). Drugs mentioned above, forms of their application, and recommended dosing are briefly summarized in the Table 1.

Table 1. Treatments of eosinophilic type of asthma (modified according to Ref. 24)

TARGET	THERAPY	ADMINISTRATION ROUTE	DOSING
IL-5	mepolizumab reslizumab	s.c. i.v.	100 mg every 4 wk 3 mg/kg once every 4 wk
IL-5 receptor α	benralizumab	s.c.	100 mg every 4–8 wk
IL-4 receptor α	dupilumab pitakinra	s.c. no further development	300 mg every 1–2 wk
IL-13	lebrikizumab tralokinumab	s.c. s.c.	250 mg monthly 300 mg every 2–4 wk
IgE	quilizumab ligelizumab omalizumab	no further development i.v., s.c. s.c.	0.1–10 mg/kg, 0.2–4 mg/kg every 2 wk 150–375 mg every 2 or 4 wk

Antagonists of lipid mediators

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) is receptor for prostaglandin D2 (PGD2) expressed on lymphocytes, eosinophils, basophils, and airways epithelial cells. Stimulation of this receptor leads to chemotaxis of inflammatory cells and release of cytokines and mediators, as well as differentiation of epithelial cells. In patients with severe asthma PGD2 count is increased in bronchoalveolar lavage fluid. **Fevipiprant**, p.o. CRTH2 antagonist, is subject of clinical trials at the moment (25).

Airway epithelium as a target

Alarmins like thymic stromal lymphoprotein (TSLP), IL-25 and IL-33 released from airway epithelial cells together with other mediators and cytokines could be other potential therapeutic targets. Among them, anti-TSLP strategy can effectively target the impaired epithelial-inflammatory crosstalk. **Tezepelumab** (AMG 157) successfully achieved primary and secondary endpoints of Phase IIb, thus might be a first-in-class drug for asthma in future (26).

Non-eosinophilic (Th2-low) asthma

This type of asthma is characterized by lack of Th2 cells and Th2-associated cytokines and by presence of neutrophil, pauci-granulocytic (eosinophil and neutrophil counts normal), or mixed (neutrophil/eosinophil) type of inflammation (1, 27). Neutrophil infiltration contributes to asthma severity, airway damage linked with neutrophilia promote goblet cell hyperplasia and, consequently, mucus overproduction, AHR, and remodelling. However, it remains unclear whether the neutrophilia is caused by chronic respiratory infections, changes in the airway microbiota, or administration of CS, impairing neutrophil apoptosis (27, 28). Non-eosinophilic inflammation occurs in about 50% of asthma patients who respond poorly to CS. In spite of this fact, majority of novel therapeutic strategies target the T2-high asthma and just few approaches target the non-eosinophilic asthma. Neutrophilic inflammation can be theoretically blocked *via* the pathways, which regulate neutrophil accumulation in the airways, *e.g.* by influencing leukotriene B₄, TNF α , IL-1, IL-6, IL-8, IL-23, and IL-17. However, none of these signalling pathways have been successfully blocked (28).

Inhibition of chemokine receptors

The chemokine receptor CXCR2 plays a critical role in neutrophil migration, while an increased level of IL-8 in the airways correlates with higher exacerbation rate. IL-8 binds to CXCR1 receptor (low affinity receptor) and CXCR2 (high affinity receptor), which stimulates the neutrophil migration to the site of inflammation. Although some preclinical trials showed promising results, administration of CXCR2 blocking agent **navarixin**, exerted only modest improvement in asthma control (Phase II) (29).

Targeting IL-17

As mentioned above, Th17 polarization of immune cells and consequent overproduction of Th17 related cytokines (IL-17A, IL-17F) are associated with more severe asthma, often correlating with airway neutrophils. However, clinical trials on **brodalumab** binding to IL-17RA receptor (mutual receptor for IL-17A and IL-17F) and on **secukimab**, an anti-IL-17A antibody, have been terminated. Thus, despite the discovery of Th17 cells and related IL-17 cytokine threw light on the asthma pathophysiology, targeting IL-17 has failed (30, 31).

TNF α blockers

Drugs targeting TNF α , *e.g.*, **infliximab**, **etanercept**, and **golimumab**, have been used in rheumatoid arthritis and other autoimmune disorders. However, these agents did not show any significant improvement in asthma, although some studies suggested that asthmatics with the history of sinusitis and asthma onset after 12 years might benefit from this drug. Nevertheless, this drug class appears to be very unlikely to become a treatment for asthma due to serious adverse effects of aforementioned drugs (infections and malignancies) (32–37).

Anti-IL-6 antibodies

IL-6 promotes Th17 cell differentiation, inversely correlates with FEV₁ and, thus, contributes to severe asthma. Targeting this cytokine with **tocilizumab** led to improvements in rheumatoid arthritis and Crohn's disease, however, it has not been tested in asthma to date (38, 39).

Targeting 5-lipoxygenase-activating protein (FLAP)

Other promising approach could be blocking of leukotriene (LT)B₄, known as a neutrophil chemoattractant. However, despite reduction in the sputum LTB₄ no significant improvement in the clinical outcomes was found. On the other hand, asthmatics with the history of nasal polyps or aspirin-associated asthma patients may benefit from this therapy (40).

Macrolides

Macrolide antibiotics appeared to be effective off-label strategy in a very small and specific subset of asthmatics. Several studies have revealed improved quality of life and reduced exacerbation. The drawbacks include potential anti-microbial resistance, however, novel macrolides lacking antimicrobial activity have been under development (41–44).

In summary, none of the above-mentioned interventions targeting non-eosinophilic asthma has proven to be successful in large clinical studies, probably due to heterogenous selection of patients or poor understanding the pathophysiology.

Other therapeutic options for asthma

Statins

Statins (or HMG-CoA reductase inhibitors) block HMG-CoA reductase involved in the synthesis of mevalonate, a precursor to cholesterol, and thereby decrease cholesterol levels. Moreover, they reveal pleiotropic effects including anti-oxidative and anti-inflammatory properties. In preclinical studies, statins reduced AHR and airway remodelling, however, multiple retrospective and prospective studies were not coherent (45, 46).

Targeting kinases and transcription factors

Many inflammatory proteins are regulated by pro-inflammatory transcription factors (TF), such as nuclear factor (NF)- κ B, activator protein (AP)-1, signal transduction-activated transcription factor (STAT)-6, GATA-3 etc. Whereas these are regulated by kinase-signalling pathways, kinases play a critical role in signal transduction and amplification of the inflammatory response and targeting kinases or transcription factors seems to be a logical approach to the treatment of asthma. However, only few kinases have entered the clinical trials where many of them had to be discontinued due to side effects or ineffectiveness (47).

Higher levels of **NF- κ B** found in bronchial biopsy specimens from asthma patients, inhibition of NF- κ B -induced gene transcription by CS, a mainstay therapy of asthma, as well as promising results from several experimental studies suggest that targeting NF- κ B might be a valuable approach to treat asthma or/and to restore CS-sensitivity (48, 49).

GATA-3 is a critical TF of type-2 response, regulating Th2 cell proliferation and production of Th2-associated cytokines (IL-4, IL-5, IL-9, and IL-13). Moreover, GATA-3 is expressed on effector cells in allergic inflammation and its level is increased in T-cells, correlating with increased IL-5 expression and AHR. Inhaled **SB010**, an DNzyme able to cut and inactivate GATA-3 mRNA, reduced early- and late-phase reactions to allergen and markers of Th2 inflammation (Phase II), however, additional clinical trials need to be conducted (50, 51).

STAT-6, activated by IL-4, IL-5, and IL-13 and regulating the Th2 inflammatory response represents another attractive intervention to reduce type-2 inflammation (52).

Targeting phosphodiesterases (PDE)

Besides anti-inflammatory effects, PDE inhibitors possess CS-sparing effect (reduction in administered CS dose). In asthma, SR forms of non-selective PDE inhibitor **theophylline** have been used as add-on therapy. **Roflumilast**, a once-daily selective PDE4-inhibitor, has been approved for treatment of COPD and it is proposed to be also effective in asthma. However, use of roflumilast in treating uncontrolled asthma requires further investigations in preclinical and clinical conditions (53, 54). In order to overcome the drawback of potential adverse effects, inhaled form of PDE4 inhibitor appears to be promising, while **CHF6001** dry powder for inhalation is being clinically tested (Phase II) (55). However, other selective PDE inhibitors might be also of benefit (56).

Targeting NO metabolism

In addition, AHR in asthma can be reduced by substances influencing the NO metabolism, such as inhibitors of NO synthases (57) or red wine polyphenolic compounds (58).

Resolution phase of the inflammation

Resolution phase of the inflammatory response is coordinated by a group of lipid mediators, specialized pro-resolving mediators (SPMs). SPMs help to restore homeostasis in a damaged tissue, therefore, analogues of SPMs seem to be another promising approach (59).

CONCLUSIONS

New treatments targeting specific inflammatory response pathways in asthma are now available or under the development. However, these novel approaches are still cost consuming and, thus, reserved only for those who have failed to respond to conventional treatment. Nevertheless, more detailed understanding of asthma phenotypes/endotypes, identifying more reliable biomarkers, molecular differences among the individuals, and consequent stratification of patients are needed. For future, huge effort is required to understand the mechanisms underlying non-eosinophilic asthma to identify targets for an adequate treatment.

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