Original Article: Emerging Targeted Therapies in Asthma: Biologics, Small Molecules, and Innovative Inhaled Formulations

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ABSTRACT

Asthma is a chronic inflammatory disease of the airways characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. This condition affects millions worldwide, leading to significant morbidity and healthcare costs. Traditional therapies, such as inhaled corticosteroids (ICS) and bronchodilators, have long been the cornerstone of asthma management. These medications primarily aim to reduce inflammation and relax airway muscles, providing symptomatic relief and preventing exacerbations. However, a subset of patients with severe asthma remains inadequately controlled despite optimal conventional therapy. This unmet need has spurred the development of novel pharmacological agents targeting specific pathways involved in asthma pathophysiology. These novel drugs include biologics, small molecules, and new inhaled formulations. Biologics, such as anti-IL-5, anti-IL-4/IL-13, and anti-IgE therapies, offer targeted treatment options for patients with severe asthma by modulating specific immune responses. Small molecule drugs, like PDE4 inhibitors and tyrosine kinase inhibitors, provide new mechanisms to control inflammation and bronchoconstriction. Additionally, advancements in inhaler technology and formulation have led to the development of new inhaled therapies, improving drug delivery and efficacy. This review discusses these novel drugs, highlighting their mechanisms of action, efficacy, and safety profiles, offering hope for better asthma management and improved patient outcomes.

Introduction

Asthma affects over 300 million people worldwide, posing a significant burden on healthcare systems and patients' quality of life. Conventional treatments, such as inhaled corticosteroids (ICS) and bronchodilators, have been effective for many patients by reducing inflammation and relieving bronchoconstriction. However, these treatments do not adequately control symptoms in all patients, particularly those with severe asthma, which is often characterized by frequent exacerbations,

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persistent symptoms, and a higher risk of adverse outcomes despite high-dose ICS and additional controller therapies [1].

The emergence of novel drugs offers new hope for these individuals. These innovative therapies are mentioned in Table 1.

1. Biologics

Biologics represent a significant advancement in the treatment of asthma, particularly for patients with severe and refractory forms of the disease. These agents are designed to target specific molecules involved in the inflammatory process that characterizes asthma, providing a more precise therapeutic approach. The development and use of biologics have shifted the treatment paradigm for severe asthma, offering new hope for patients who do not respond adequately to conventional therapies. However, they come with disadvantages such as high cost, inconvenient administration via injection or infusion, potential side effects (e.g., infections, allergic reactions), limited long-term safety data, and accessibility challenges, particularly in low-income regions (Figure 1).

1.1. Anti-IL-5 Therapies

Anti-IL-5 therapies target interleukin-5 (IL-5), a cytokine essential for the growth, differentiation, recruitment, activation, and survival of eosinophils. Eosinophils are significant inflammatory cells involved in various asthma phenotypes, particularly eosinophilic asthma. By inhibiting IL-5, these therapies reduce eosinophil levels in the blood and tissues, leading to decreased inflammation and improved asthma control.

Anti-IL-5 therapies are generally well-tolerated, with the most common side effects being injection site reactions, headache, and back pain. Long-term safety data are still being collected, but current evidence suggests a favourable safety profile [1].

In practice, these therapies are particularly beneficial for patients with severe eosinophilic asthma who do not respond adequately to standard treatments, including high-dose inhaled corticosteroids and long-acting beta-agonists. They represent a significant advancement in personalized asthma care [2].

Mepolizumab is an anti-IL-5 monoclonal antibody that binds to IL-5, preventing it from interacting with its receptor on the surface of eosinophils. Clinical trials have shown that mepolizumab significantly reduces asthma exacerbations and improves asthma control in patients with eosinophilic asthma [1].

Reslizumab similar to mepolizumab, is an anti-IL-5 monoclonal antibody that has demonstrated significant efficacy in reducing asthma exacerbations and improving lung function in patients with elevated blood eosinophils [3].

Benralizumab targets the IL-5 receptor alpha on eosinophils and basophils, leading to their depletion via antibody-dependent cell-mediated cytotoxicity. This results in a rapid and nearly complete reduction of eosinophils. Clinical studies have shown that benralizumab significantly reduces exacerbations and improves lung function in patients with severe eosinophilic asthma [4].

1.2. Anti-IL-4/IL-13 Therapies

Anti-IL-4/IL-13 therapies, while effective in targeting allergic inflammation and asthma, have several disadvantages. These include high cost, potential side effects such as injection site reactions and increased risk of infections, and limited long-term safety data. Additionally, these therapies may not be effective for all patients, especially those without a significant Th2-driven component in their asthma [5,6].

Dupilumab is a monoclonal antibody that targets the IL-4 receptor alpha subunit, thereby inhibiting the signalling of both IL-4 and IL-13.

Clinical trials have shown that dupilumab significantly improves lung function, reduces exacerbations, and enhances quality of life in patients with moderate-to-severe asthma, particularly those with a high type 2 inflammation profile [6].

1.3. Anti-IgE Therapy

Anti-IgE therapy, targets immunoglobulin E (IgE), a key mediator in allergic asthma. While effective, it has several disadvantages. These include high cost, potential for injection site reactions, and rare but serious side effects such as anaphylaxis. Additionally, it requires regular subcutaneous injections, which can be inconvenient for patients. There is also variability in patient response, with some not experiencing significant benefits [7].

Omalizumab is a monoclonal antibody that binds to free IgE, preventing it from binding to its receptor on mast cells and basophils. This inhibition reduces the allergic response and subsequent asthma symptoms. Omalizumab has been used for several years and has a well-established efficacy and safety profile in the treatment of moderate-to-severe allergic asthma. It has been shown to significantly reduce the frequency of exacerbations and improve overall asthma control [8,9].

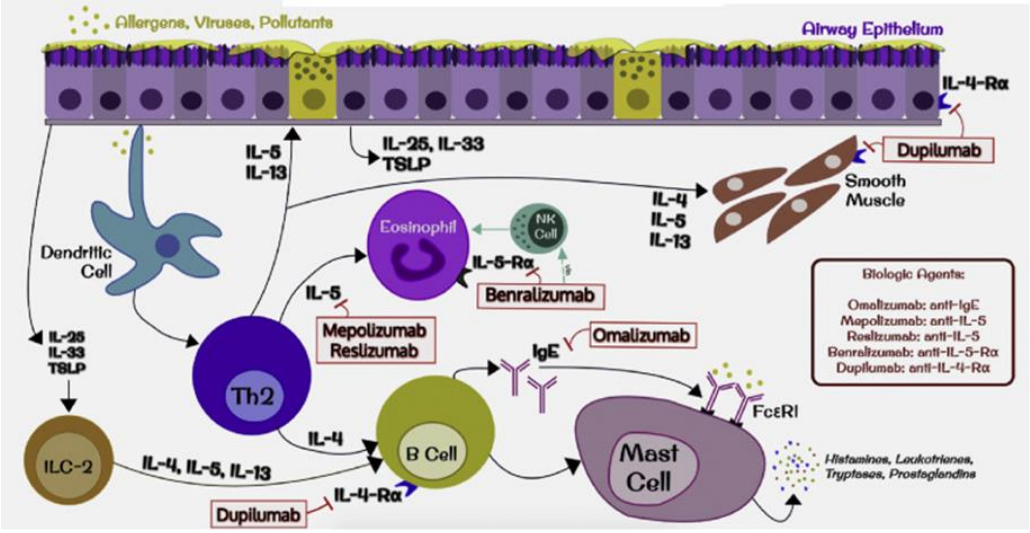

Figure 1. Mechanism of action of Biologics

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2. Small Molecules

Small molecule drugs, such as leukotriene receptor antagonists (e.g., montelukast) and phosphodiesterase inhibitors (e.g., roflumilast), offer the advantage of oral administration, targeting intracellular signaling pathways involved in inflammation and bronchoconstriction. These drugs are generally easier and less expensive to manufacture and administer compared to biologics, making them a valuable addition to the asthma treatment arsenal. They can effectively reduce inflammation and improve lung function, providing an accessible option for many patients [10, 11].

2.1. Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRAs) like montelukast and zafirlukast, offer the advantage of oral administration, targeting the leukotriene pathway involved in inflammation and bronchoconstriction. LTRAs block the action of leukotrienes, which are inflammatory

mediators contributing to asthma symptoms. These drugs are generally easier and less expensive to manufacture and administer compared to biologics, making them a valuable addition to the asthma treatment arsenal. LTRAs can effectively reduce inflammation, prevent bronchoconstriction, and improve lung function, providing an accessible option for many patients [12,13].

2.1. Phosphodiesterase-4 (PDE4) Inhibitors

Phosphodiesterase-4 (PDE4) is an enzyme that specifically breaks down cyclic adenosine monophosphate (cAMP) into AMP, thereby regulating the intracellular levels of cAMP. cAMP is a crucial second messenger involved in various cellular processes, including the modulation of inflammatory responses. PDE4 inhibitors inhibit the activity of the PDE4 enzyme, leading to an increase in intracellular cAMP levels. The elevated cAMP levels exert multiple anti-inflammatory effects, which are particularly beneficial in treating chronic inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and psoriasis. Roflumilast is a selective PDE4 inhibitor primarily approved for the treatment of chronic obstructive pulmonary disease (COPD), but it has also shown promise in asthma management. By inhibiting PDE4, roflumilast reduces the breakdown of cAMP, leading to anti-inflammatory effects. Studies have demonstrated that roflumilast can improve lung function and reduce the frequency of exacerbations in patients with asthma, particularly those with a neutrophilic phenotype [14].

2.2. Tyrosine Kinase Inhibitors

Tyrosine kinases are a group of enzymes that phosphorylate specific proteins on tyrosine residues, which is a crucial step in the activation of various signaling pathways. These enzymes play a pivotal role in regulating cellular processes, including growth, differentiation, metabolism, and immune responses. In the context of asthma, tyrosine kinases are involved in the activation and survival of inflammatory cells that contribute to the pathophysiology of the disease. Masitinib is a tyrosine kinase inhibitor that targets several kinases involved in the pathophysiology of asthma, including those associated with mast cell activation. Clinical trials have shown that masitinib can improve asthma control and reduce symptoms in patients with severe, corticosteroid-dependent asthma. The drug's ability to inhibit multiple pathways simultaneously makes it a promising candidate for treating severe asthma [15].

2.3. CRTh2 Antagonists

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2), also known as DP2, is a G-protein-coupled receptor that is primarily expressed on Th2 cells, eosinophils, basophils, and other immune cells. Prostaglandin D2 (PGD2) is a lipid mediator produced mainly by mast cells and acts as a potent chemoattractant through its interaction with the CRTh2 receptor. CRTh2 antagonists block the interaction between PGD2 and the CRTh2 receptor, thereby inhibiting the recruitment and activation of Th2 cells and eosinophils. This blockade helps to reduce inflammation and improve asthma symptoms. Fevipiprant is an oral CRTh2 antagonist that has shown potential in reducing airway inflammation and improving asthma control. Clinical studies have indicated that fevipiprant can reduce sputum eosinophil counts and improve lung function in patients with moderate-to-severe asthma, particularly those with an eosinophilic phenotype [16].

2.4. Janus Kinase (JAK) Inhibitors

Janus kinases (JAKs) are a family of intracellular, non-receptor tyrosine kinases

that play a pivotal role in the signaling pathways of various cytokines and growth factors. There are four main JAKs: JAK1, JAK2, JAK3, and TYK2. These enzymes are essential for the signaling of cytokines through their respective receptors, leading to the activation of downstream signaling pathways, including the Signal Transducer and Activator of Transcription (STAT) proteins. JAK inhibitors are small molecules that specifically target and block the activity of JAK enzymes. By inhibiting JAKs, these drugs prevent the phosphorylation and activation of STAT proteins, thereby blocking the downstream signaling of cytokines that contribute to the inflammatory process in asthma.

Tofacitinib is a JAK inhibitor that has been explored for its potential in asthma treatment. By inhibiting JAK enzymes, tofacitinib can reduce the signaling of cytokines such as IL-4, IL-5, and IL-13, leading to decreased inflammation and improved asthma control. Early clinical trials have shown promising results, but further research is needed to establish its efficacy and safety in asthma patients [17].

3. Novel inhaled therapies

Advancements in inhaler technology and formulations have led to the development of new inhaled therapies that offer improved delivery and efficacy. These novel inhaled therapies are designed to enhance drug delivery to the lungs, improve patient adherence, and provide better control of asthma symptoms with potentially fewer side effects.

3.1. Long-Acting Beta-Agonists (LABAs) and Corticosteroid Combinations

Combination inhalers that include a long-acting beta-agonist (LABA) and an inhaled corticosteroid (ICS) are a cornerstone of asthma management. These combinations offer the convenience of two medications in one inhaler, improving adherence and ensuring consistent delivery of both components.

Fluticasone furoate/vilanterol is a once-daily combination inhaler that provides prolonged asthma control. Clinical trials have demonstrated that this combination significantly improves lung function and reduces the risk of exacerbations compared to ICS alone [18]. The once-daily dosing schedule enhances patient adherence, making it a practical option for long-term asthma management.

3.2. Triple Therapy Inhalers

Triple therapy inhalers combine three types of medications: an inhaled corticosteroid (ICS), a long-acting beta-agonist (LABA), and a long-acting muscarinic antagonist (LAMA). This combination provides comprehensive control of asthma symptoms through multiple mechanisms, targeting various aspects of the disease's pathophysiology. The goal of triple therapy is to improve lung function, reduce exacerbations, and enhance overall asthma control, particularly in patients with severe or poorly controlled asthma. Trelegy Ellipta is an example of a triple therapy inhaler that combines fluticasone furoate, vilanterol, and umeclidinium. This inhaler has shown superior efficacy in improving lung function, reducing exacerbations, and enhancing quality of life compared to dual therapy (ICS/LABA) inhalers [19]. By addressing different pathways involved in asthma, triple therapy inhalers provide a robust option for patients with severe or uncontrolled asthma.

3.3. Ultra-Long-Acting Beta-Agonists (ULABAs)

Ultra-long-acting beta-agonists (ULABAs) are a class of bronchodilators that provide extended bronchodilation, typically lasting 24 hours or more. This extended duration of action allows

for once-daily dosing, improving patient adherence and convenience compared to shorter-acting bronchodilators. ULABAs are used in the management of asthma and chronic obstructive pulmonary disease (COPD), providing sustained symptom relief and enhancing overall disease control. ULABAs work by selectively binding to beta-2 adrenergic receptors on the smooth muscle cells lining the airways. This binding activates adenylate cyclase, increasing intracellular cyclic AMP (cAMP) levels. Elevated cAMP leads to the relaxation of smooth muscle cells, resulting in bronchodilation. The prolonged binding and activation of beta-2 receptors by ULABAs result in sustained bronchodilation, reducing the need for frequent dosing. Indacaterol is an ULABA that provides 24-hour bronchodilation with once-daily dosing. Although primarily used in COPD, indacaterol has potential applications in asthma management, particularly in patients who benefit from consistent bronchodilation. Studies have shown that indacaterol improves lung function and reduces the need for rescue medications in asthma patients [20].

3.4. Novel Inhaler Devices

Innovations in inhaler devices aim to enhance drug delivery efficiency, ease of use, and patient adherence. These devices often incorporate features such as dose counters, feedback mechanisms, and improved aerosol delivery systems.

Smart inhalers are equipped with sensors and connectivity features that monitor medication usage and provide feedback to patients and healthcare providers. These devices can track inhalation technique, adherence, and provide reminders, helping to optimize asthma management [21]. Smart inhalers have been shown to improve adherence and asthma control, reducing the frequency of exacerbations and healthcare utilization.

3.5. Breath-Actuated Inhalers

Breath-actuated inhalers activate automatically upon inhalation, ensuring that medication is released at the optimal point in the breathing cycle. This design minimizes coordination issues and improves drug delivery to the lungs.

This inhaler combines beclometasone (an ICS) and formoterol (a LABA) in a breath-actuated device. Studies have shown that this inhaler improves lung function and asthma control, particularly in patients who struggle with traditional metered-dose inhalers (MDIs) [22].

In summary, advancements in inhaler technology and formulations have led to the development of novel inhaled therapies that offer improved delivery and efficacy. These innovations provide new options for asthma management, enhancing patient adherence, and optimizing drug delivery to the lungs, ultimately improving asthma control and patient outcomes.

4. Asthma Medication Prices in India

The cost of asthma medications in India can vary significantly based on the type of drug, its brand, and the form in which it is administered. The following provides an overview of the typical prices for commonly used asthma treatments:

a) **Inhaled Corticosteroids (ICS)**

Beclomethasone Dipropionate: ₹200-₹300 per inhaler.

Budesonide: ₹250-₹400 per inhaler.

b) **Long-Acting Beta-Agonists (LABA)**

Salmeterol: Often combined with ICS, around ₹500-₹700 per combination inhaler.

c) **Combination Inhalers (ICS + LABA)**

Fluticasone/Salmeterol (Seretide): ₹600-₹900 per inhaler.

Budesonide/Formoterol (Symbicort): ₹500-₹800 per inhaler.

d) **Short-Acting Beta-Agonists (SABA)**

Salbutamol (Albuterol): ₹100-₹200 per inhaler.

e) **Leukotriene Receptor Antagonists**

Montelukast: ₹50-₹150 for a month's supply (typically 30 tablets).

f) **Biologics**

Omalizumab (Xolair): ₹18,000-₹25,000 per dose (administered bi-weekly or monthly).

Mepolizumab (Nucala): Approximately ₹50,000 per dose.

g) **CRTh2 Antagonists**

Fevipiprant (Not widely available yet): Prices not established in India.

The above prices are approximations and can vary depending on the pharmacy, location, and whether the medication is purchased as a generic or brand-name product. Furthermore, prices may be influenced by insurance coverage and government subsidies, such as those provided under the *Ayushman Bharat Yojana program (Government of India),* which aims to make essential asthma medications more accessible to low-income patients [26].

Conclusion

The development of novel drugs for asthma represents a significant advancement in the management of this chronic disease. Biologics, small molecules, and innovative inhaled therapies offer new options for patients, particularly those with severe or difficult-to-treat asthma. Continued research and clinical trials will further elucidate the long-term efficacy and safety of these new treatments, potentially transforming the therapeutic landscape for asthma.

Table No. 1: Drugs used in asthma and its Pharmacological activities

Drug class	Drug name	Mechanism of action	Common side effects	References
Biologics	Omalizumab	Binds to IgE, preventing it from triggering allergic responses	Injection site reactions, anaphylaxis	[8,9]
	Mepolizumab	Binds to IL-5, reducing eosinophil levels	Headache, injection site reactions, back pain	[1]
	Reslizumab	Binds to IL-5, reducing eosinophil levels	Oropharyngeal pain, anaphylaxis	[3]
	Benralizumab	Binds to IL-5 receptor, depleting eosinophils	Headache, pharyngitis, pyrexia	[2]
	Dupilumab	Inhibits IL-4 and IL-13 signaling	Injection site reactions, conjunctivitis	[5]
Leukotriene Receptor Antagonists (LTRAs)	Montelukast	Blocks leukotriene receptors, reducing inflammation and bronchoconstriction	Headache, abdominal pain, mood changes	[12]

	Zafirlukast	Blocks leukotriene receptors, reducing inflammation and bronchoconstriction	Headache, nausea, liver dysfunction	[12]
5-Lipoxygenase Inhibitors	Zileuton	Inhibits 5-lipoxygenase, preventing leukotriene synthesis	Liver enzyme elevation, headache	[23]
Beta2-Adrenoceptor Agonists	Albuterol	Stimulates beta2-adrenergic receptors, leading to bronchodilation	Tremor, nervousness, tachycardia	[11]
	Salmeterol	Stimulates beta2-adrenergic receptors, leading to bronchodilation	Throat irritation, headache, muscle cramps	[11]
Phosphodiesterase Inhibitors	Roflumilast	Inhibits phosphodiesterase-4, reducing inflammation	Weight loss, nausea, diarrhea	[10]
Corticosteroids	Prednisone	Reduces inflammation by inhibiting multiple inflammatory pathways	Weight gain, hypertension, hyperglycaemia	[12]
	Fluticasone	Reduces inflammation by inhibiting multiple inflammatory pathways	Throat irritation, oral thrush, hoarseness	[12]
CRTh2 Antagonists	Fevipiprant	Blocks CRTh2 receptor, reducing Th2 cell and eosinophil activity	Headache, nasopharyngitis, gastrointestinal issues	[23]
	Timapiprant	Blocks CRTh2 receptor, reducing Th2 cell and eosinophil activity	Headache, dizziness, gastrointestinal issues	[24]

Conflict of Interests

The authors declare that there is no conflict of interest.

Authors' Contributions

B.A.D.N. collected literature data and drafted the first manuscript, made corrections according to inputs from co-authors. B.S.A., D.D, D.N., edited the manuscript. B.S.A. suggested the topic, supervised B.A.D.N., reviewed the manuscript. B.A.D.N., B.S.A., D.D, D.N., conducted all correspondence with the Editorial Board. All authors read and approved the final manuscript.

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