Drug Used in Treatment of Bronchial Asthma

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Bronchial Asthma

- **Bronchial asthma is a condition characterized by high responsiveness of the airway to a variety of stimuli, the result of which is widespread narrowing of the airways, that changes in severity either spontaneously or as a result of treatment (i.e: reversible).**

Bronchial Asthma

Pathology:

1. Bronchospasm leading to narrowing of the airways.
2. Mucosal edema leading to mucosal thickening and narrowing of airways
3. Mucous secretion leading to mechanical occlusion.
4. Deposition of collagen beneath the endothelium.
5. Hyperplasia of vessels, smooth muscle, secretory glands and goblet cells.

Bronchial Asthma

Characterized by:

1. **Attacks of coughing**
2. **Shortness of breath – difficulty in breathing**
3. **Chest tightness**
4. **Wheezing**

Bronchial Asthma

Bronchoconstrictors:

- **Acetylcholine, β-blockers, Adenosine, α-adrenergic agonists, Prostaglandins $F_{2\alpha}$ & D_2, Serotonin, Bradykinin, Histamine, Leukotrienes C_4 & D_4, Platelet-activating factor, …**

Inflammation:

- **Results from IgE-mediated allergy, or viral infection.**

Pathogenesis of Bronchial Asthma

Immunologic Model:

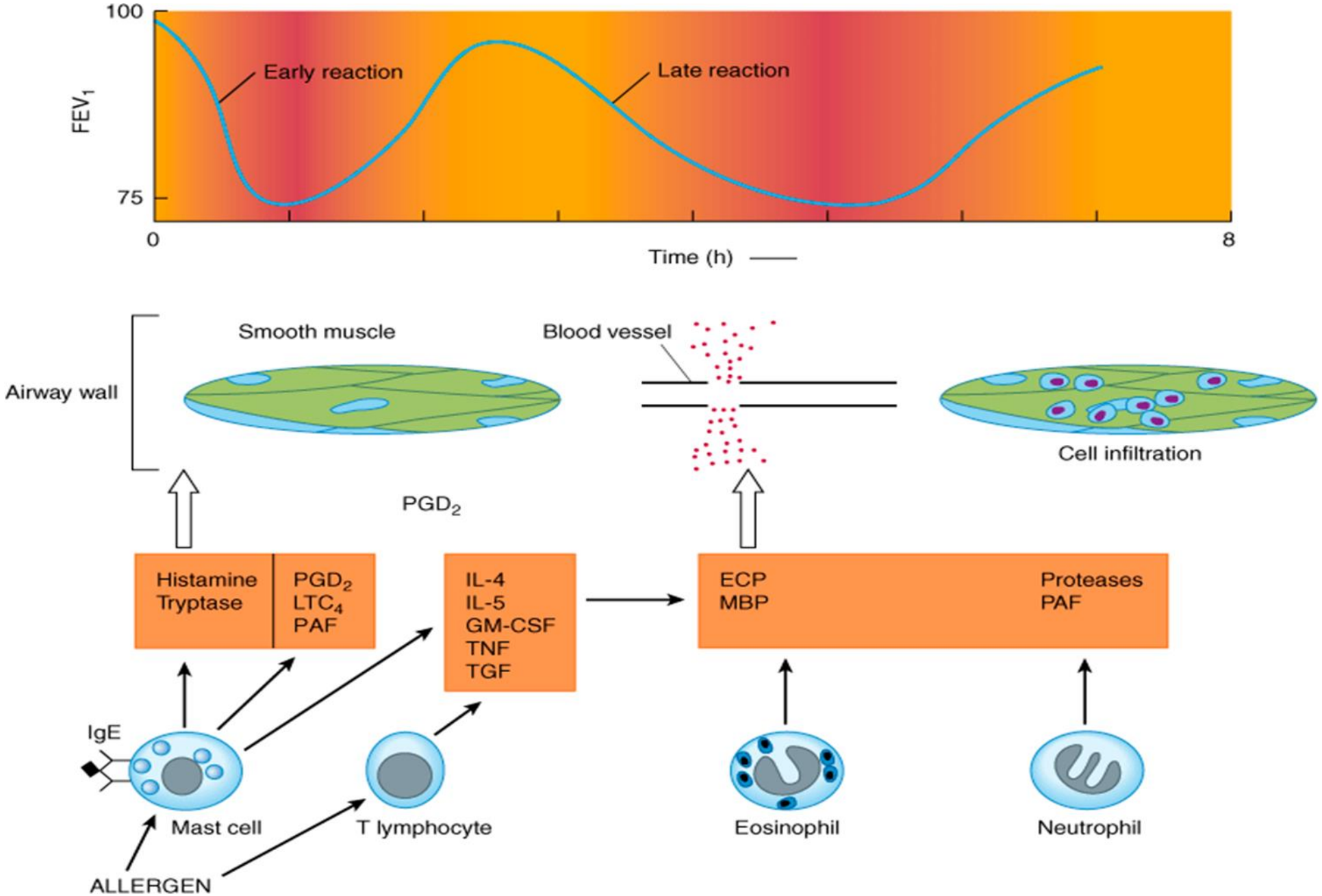
- Bronchial Asthma is mediated by IgE antibodies bound to airway mast cells.
- On re-exposure to an antigen, Ag-Ab interaction takes place on the surface of mast cells leading to release of mediators: histamine, leukotrienes C_4 & D_4, PGD_2, eosinophil chemotactic factor, neutrophil chemotactic factor and many others.
- These agents produce contraction of airway smooth muscle, mucosal edema, cellular infiltration and increased mucus secretion.

Pathogenesis of Bronchial Asthma

- **Bronchoconstriction appearing within 10-20 min of exposure to a provoking factor and mediated by the release of bronchoconstrictors from mast cells is called the “early asthmatic response”.**
- **In some patients a “late asthmatic response” may occur 3-6 hours after exposure and is due to airway inflammation, cellular infiltration of airway mucosa, mucous hypersecretion and sustained bronchoconstriction.**

Pathogenesis of Bronchial Asthma

- **Eosinophiles are involved in this response through generation of eosinophil major basic protein and eosinophil cationic protein which produce epithelial sloughing and increase in the contractile responsiveness of the airway smooth muscle.**
- **Cytokines produced by T_{H2} lymphocytes, GM-CSF, TNF, TGF, Interleukins 4, 5, 9, 13 attract and activate eosinophiles and neutrophiles, stimulate IgE production by B lymphocytes, and stimulate mucus production by bronchial epithelial cells.**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Pathogenesis of Bronchial Asthma

- **A major limitation to this classic conception of asthma as an allergic disease is that it applies only to a subgroup of patients with evidence of allergy.**
- **The allergen challenge model fails to account for all the features of the condition even in allergic asthmatics.**
- **Allergic asthma accounts for a great proportion of asthma that develops in childhood, but a smaller proportion of adult-onset asthma.**

Pathogenesis of Bronchial Asthma

- **Thus, modifying terms to describe asthma in different patients include: “extrinsic” *vs* “intrinsic,” “aspirin-sensitive,” “adult-onset,” “post-viral,” and “obesity-related.”**
- **Many pathways and mechanisms other than production of IgE and activation of mast cell degranulation are involved in asthma’s pathogenesis, and most asthma attacks are not triggered by inhalation of allergens, but instead by viral respiratory infections.**

Drugs Used for treatment of Bronchial Asthma

1. Sympathomimetics
2. Methylzanthines
3. Antimuscarinic agents
4. Corticosteroids
5. Inhibitors of mast cell degranulation
6. Leukotriene pathway inhibitors
7. Targeted (monoclonal antibodies) therapy

Sympathomimetics (β_2-Adrenergic Receptors Selective Drugs)

- They are the most widely used agents for the treatment of acute bronchoconstriction.
- They are given by inhalation or nebulization.

They include:

1. Fast-acting β_2-Agonists (FABs) (albuterol and terbutaline): Bronchodilation is maximal within 15 minutes and persists for 3 - 4 hours.
2. Long-acting β_2-Agonists (LABAs) (salmeterol and formoterol): durations of action ~ 12 hour . They have high lipid solubility.

Sympathomimetics (β_2-Selective Drugs)

- Because they have no anti inflammatory action, they should not be used as monotherapy for asthma, and should be combined with corticosteroids.

3. Ultralong-acting β_2-agonists (Indacterol, vilanterol and others): given once a day.

- Because their prolonged bronchodilation masks symptoms of bronchial inflammation, they should be used only in combination with an inhalational corticosteroids (ICS).
- They may be used as monotherapy for treatment of chronic obstructive pulmonary disease (COPD).

Sympathomimetics (β_2-Selective Drugs)

Pharmacological actions:

- **Increase cAMP levels in bronchial smooth muscle by stimulating adenylyl cyclase**
- **Considered the main stay of treatment of bronchial asthma**

1. **Relaxation of airway smooth muscle leading to bronchodilation.**
2. **Inhibition of the release of bronchoconstrictor substances from mast cells.**
3. **May inhibit microvascular leak.**
4. **May increase mucociliary transport by increasing ciliary activity.**

Sympathomimetics (β_2-Selective Drugs)

Additional Therapeutic Uses:

1. **To inhibit the uterine contractions associated with premature labor.**
2. **Chronic obstructive pulmonary disease.**

Sympathomimetics (β_2-Selective Drugs)

Adverse Reactions:

1. Lactic acidosis that probably reflects a direct effect of β_2-agonists on cellular metabolism rather than tissue hypoxia. It may contribute to dyspnea.
2. They drive potassium into the cells leading to hypokalemia by increasing the activity of the Na^+/K^+-ATPase pump in skeletal muscle. Skeletal muscle tremor, occasional weakness.
3. Tachyphylaxis: a reduction in response can be seen after several days of regular use.

Methyxanthines (Theophylline)

- **Methyxanthines include theophylline, caffeine and theobromine.**
- **The use of theophylline, once a mainstay of asthma treatment, has almost ceased with demonstration of the greater efficacy of inhaled β_2-agonists and inhaled glucocorticoids.**
- **Accelerating this decline in theophylline's use are its toxicities (nausea, vomiting, tremulousness, convulsions, arrhythmias) and drug-drug interactions and the requirement for monitoring serum concentration because of its narrow therapeutic index.**
- **However, it may still be used to treat apnea in premature infants, and occasional patients with bronchial asthma.**

Antimuscarinic Agents

1. **Short acting (4 hours): Ipratropium bromide**
2. **Long acting (24 hours or more): Tiotropium bromide**

- **They are derivatives of atropine.**
- **They are quaternary ammonium compounds (+), not suitable for oral administration**
- **Block airway smooth muscle contraction and the increase of mucus secretion produced by acetylcholine, through actions on M_3 muscarinic receptors.**

Antimuscarinic Agents

- **Usually administered by inhalation, and the action is confined to the airway.**
- **Do not cross the blood brain barrier.**
- **Do not inhibit mucociliary clearance, in contrast to atropine, which avoids accumulation of secretions.**
- **The magnitude of action is proportional to the contribution of parasympathetic stimulation to airway smooth muscle tone in asthmatic patients.**

Antimuscarinic Agents

- Mainly used for treatment of COPD with a reversible obstruction component.
- Cab be used in bronchial asthma and can be combined with other drugs.

Adverse reactions:

- Dry mouth, which can be managed with the use of a spacer to reduce oropharyngeal deposition, or by dose reduction.
- Anticholinergic use may be associated with increased risk of dementia with advancing age (?).

Modulators of Airway inflammation

1. Inhaled corticosteroids.
2. Mast cell stabilizers.
3. Leukotriene pathway inhibitors.
4. Monoclonal Antibodies.

Corticosteroids

- **Inhalation is a major breakthrough in asthma therapy:**
  Beclomethasone diproprionate, Triamcinolone acetonide, Budesonide, Flunisolide, Fluticasone
- **Systemic: Prednisone PO, Methylprednisolone IV**
- **Corticosteroids in combination with β_2-agonists are first-line therapy of bronchial asthma.**

Inhaled corticosteroids

- **Action starts after several hours.**
- **Most important action is inhibition of infiltration of asthmatic airways by lymphocytes, eosinophiles and mast cells.**
- **Inhibit production of pro-inflammatory cytokines.**
- **Inhibit phospholipase A_2 and thus the synthesis of arachidonic acid metabolites (PGs & LTs).**
- **May inhibit IgE synthesis(?!)**

Inhaled corticosteroids

- **Do not relax airway smooth muscle but reduce bronchial hyper-reactivity (by prolonged therapy), reduce asthma exacerbations if used regularly, and can restore the effectiveness of β_2-agonists.**
- **Do not relief the acute episode.**
- **Improve all indices of asthma control: severity of symptoms, frequency of attacks and quality of life.**
- **Their effect on airway obstruction may be due in part to their contraction of engorged vessels in the bronchial mucosa.**

Inhaled corticosteroids

Adverse effects:

In addition to the systemic adverse effects,

1. **Oropharyngeal candidiasis.**
2. **Dysphonia (hoarseness of voice) – local effect on vocal cords.**
3. **Suppression of hypothalamic-pituitary-adrenal axis.**

Mast Cell Stabilizers

Cromolyn Na, Nedocromil Na:

- They were once widely used for asthma management, especially in children, but have now been supplanted by other therapies.
- These drugs act by inhibiting mast cell degranulation.
- They have no direct bronchodilator action, but inhibit both antigen and exercise-induced bronchospasm in asthmatic patients.
- Solutions of cromolyn are available for nebulization.
- Cromolyn is available for allergic rhinoconjunctivitis and other mast disorders as a nasal spray (OTC) and oral solution.
- Both drugs can be prescribed as ophthalmic solutions.

Leukotriene Pathway Inhibitors

- Leukotrienes are synthesized by many inflammatory cells in the airways: eosinophiles, mast cells, macrophages and basophiles.
- Leukotriene B_4 (LTB_4) is a potent neutrophile chemoattractant, and LTC_4, and LTD_4 exert bronchoconstriction, increased bronchial reactivity, mucosal edema, and mucus hypersecretion.

Leukotriene Pathway Inhibitors

These effects can be interrupted by:

1. **5-Lipoxygenase inhibitors: Zileuton.**

   Block production of LTC_4, LTD_4, LTE_4, LTB_4.

2. **LTD_4 receptor antagonists: Zafirlukast, Montelukast**

- **There are NOT first-line agents for bronchial asthma.**

Leukotriene Pathway Inhibitors

- **Both improve asthma control and reduce frequency of exacerbations.**
- **Both are effective in blocking airway response to exercise, aspirin and antigen challenge.**
- **They were shown to be effective when taken regularly in outpatients.**
- **Overall effect is less than that of inhaled corticosteroids, but equally effective in reducing frequency of exacerbations.**
- **Advantage: PO administration**

Leukotriene Pathway Inhibitors

- **Leukotrienes have an important role in aspirin-exacerbated respiratory disease (AERD), that combines the features of asthma, chronic rhinosinusitis with nasal polyposis.**
- **AERD is thought to result from inhibition of cyclooxygenase, shifting arachidonic acid metabolism from the prostaglandin to the leukotriene pathway.**
- **Therefore, leading to profound bronchoconstriction, nasal congestion.**
- **Aspirin-exacerbated respiratory disease occurs in approximately 5-10% of patients with asthma.**

Leukotriene Pathway Inhibitors

Main Adverse effects:

Zileuton: Liver toxicity, dyspepsia.

Receptor blockers:

a) **High risk of serious neuropsychiatric events, including suicidality in adults and adolescents**
b) **Nightmares and behavioral problems in children [Irritability, aggressiveness, suicidality and sleep disturbance].**
c) **Fatal hepatic failure.**

Leukotriene Pathway Inhibitors

Drug Interactions:

Zileuton: inhibition of the metabolism of theophylline, warfarin, propranolol, & terfenadine probably due to inhibition of drug metabolizing isoenzymes (CYP3A4 and others).

Receptor blockers: increased plasma concentration of warfarin due to inhibition of the cytochrome P450 2C9 by zafirlukast. Erythromycin reduces their bioavailability.

Targeted (Monoclonal Antibody) Therapy

Anti IgE Monoclonal Antibodies

Omalizumab:

- **Its specific target is the portion of IgE that binds to its receptors (FcεR1 and FcεR2 receptors) on dendritic cells, basophiles, mast cells, and other inflammatory cells.**
- **It inhibits the binding of IgE to its receptor and thus prevent mast cell degranulation.**
- **It's use is restricted to patients with moderate-to-severe asthma and evidence of perennial allergic sensitization.**

Targeted (Monoclonal Antibody) Therapy

- **It lowers free plasma IgE to undetectable levels and significantly reduces the magnitude of both early and late bronchospsatic responses to antigen challenge.**
- **It's most important clinical effect is reduction in the frequency and severity of asthma exacerbation, and reduction of corticosteroid requirements.**

Targeted (Monoclonal Antibody) Therapy

- **Patients most likely to respond are those with a history of repeated and severe exacerbations, high corticosteroid requirement, and poor pulmonary function.**
- **It has been proven effective in chronic recurrent urticaria, nasal polyposis and peanut allergy.**

Targeted (Monoclonal Antibody) Therapy

Anti IL5 Therapy

- T_2 helper cells secrete IL-5 as a proeosinophilic cytokine that results in eosinophilic airway inflammation.
- Although not central to the mechanisms of asthma in all patients, some patients with severe asthma have airway and peripheral eosinophilia, driven by upregulation of IL-5.

Targeted (Monoclonal Antibody) Therapy

- **Two humanized monoclonal antibodies targeting IL-5, mepolizumab and reslizumab, and another targeting the IL-5 receptor, benralizumab, are used for treatment of severe eosinophilic asthma.**
- **They are effective in improving pulmonary function and measures of asthma control, while preventing exacerbations in asthmatic patients with peripheral eosinophilia, as add-on therapy.**

Targeted (Monoclonal Antibody) Therapy

- **Mepolizumab may be used for treatment of eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome (HES), and rhinosinusitis with nasal polyps.**
- **These drugs may have a risk of anaphylaxis, or hypersensitivity.**
- **In addition, reactivation of herpes zoster has been reported in some patients who received mepolizumab.**

Targeted (Monoclonal Antibody) Therapy

Anti IL-4/IL-13 Therapy:

- **Dupilumab (an antibody directed against the IL-4α co-receptor for both IL-4 and IL-13)**
- **It has been shown to reduce exacerbation frequency and improve pulmonary function and measures of asthma control.**
- **May be used in patients with moderate-to-severe asthma, with an eosinophilic phenotype or corticosteroid-dependance.**

Targeted (Monoclonal Antibody) Therapy

- **It is also indicated for moderate to severe atopic dermatitis, prurigo nodularis, rhinosinusitis with nasal polyposis, and eosinophilic esophagitis.**
- **Dupilumab may cause a peripheral eosinophilia which is typically transient but in rare cases may persist.**
- **Avoid initiation if baseline eosinophils are very elevated (>1500 eosinophils/µL).**

Targeted (Monoclonal Antibody) Therapy

Anti TSLP Therapy:

- **The most recent monoclonal antibody approved for severe asthma treatment is tezepelumab-ekko.**
- **Its target is thymic stromal lymphopoietin (TSLP) which is an epithelial cytokine.**
- **Blocking the target decreases several downstream inflammation-associated cytokines (IgE, IL-5, and IL-13) and biomarkers (peripheral and airway submucosal eosinophils and fractional exhalation of nitric oxide).**

Monoclonal antibodies for use in asthma.

Antibody Name	Isotype	Target	Route of administration	Patient's age
Omalizumab	Humanized IgG1	IgE	SC every 2-4 weeks	6 years and older
Mepolizumab	Humanized IgG1	IL-5	SC every 4 weeks	6 years and older
Benralizumab	Humanized IgG1	IL-5 receptor	SC every 4 weeks for the first 3 doses, the every 8 weeks	6 years and older
Rezlizumab	Humanized IgG4	IL-5	IV infusion every 4 weeks	18 years and older
Dupilomab	Human IgG4	IL-4 receptor	SC every other week	6 years and older
Tezepelumab-ekko	Human IgG2	TSLP*	SC every 4 weeks	12 years and older

*TSLP thymic stromal lymphopoietin

These are antiinflammatory therapy targeting specific inflammatory pathways.