بسم الله الرحمن الرحيم

PHARMACOLOGY

FINAL | Lecture 3

Drugs Used in the Treatment of Bronchial Asthma (pt.2)

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﴿ وَلَقَدْ نَعْلَمُ أَنَّكَ يَضِيقُ صَدْرُكَ بِمَا يَقُولُونَ ﴿٩٧﴾ فَسَبِّحْ بِحَمْدِ رَبِّكَ وَكُن مِّنَ السَّاجِدِينَ ﴾

سبحان الله وبحمده، سبحان الله العظيم

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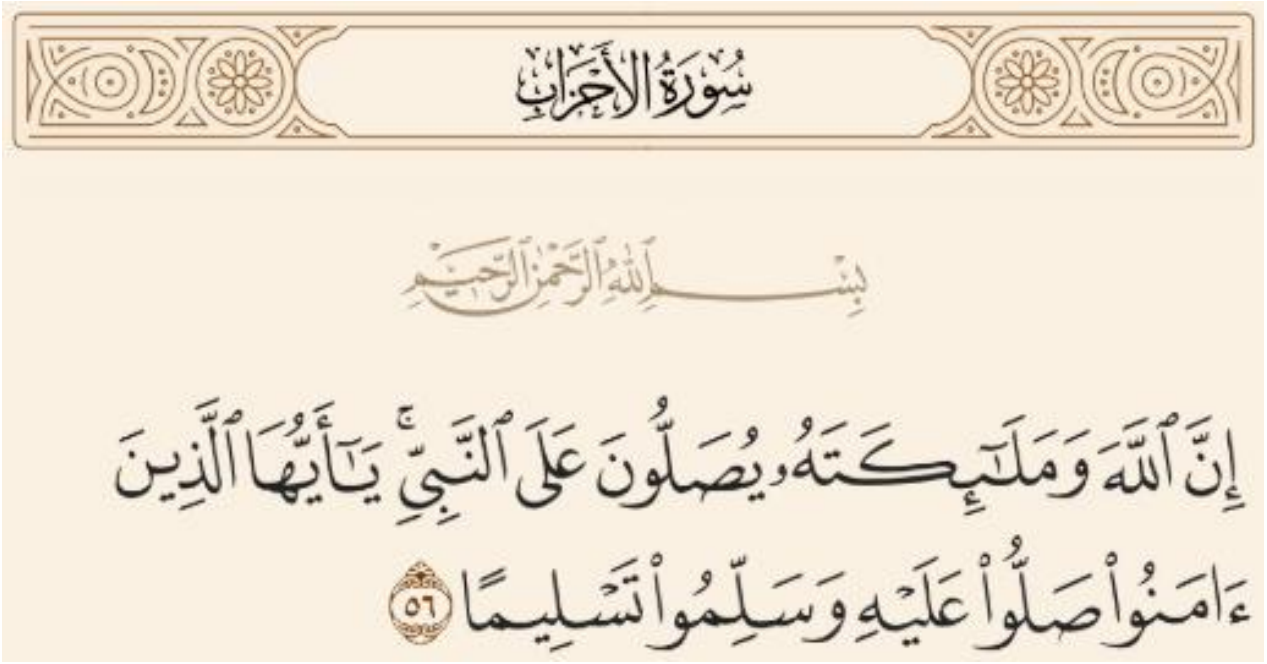
قبل أن نبدأ بهذا الملف، علينا أن نستعين بالله ولا نعجز، ونعزم ونتوكل عليه، فهو نعم المعين ونعم الوكيل.
ادخلوا على دراستكم بنيةٍ خالصةٍ لله، واجعلوا تعبكم قربة، وسعيكم طاعة، والله لا يضيع أجر من أحسن عملاً .

ولا تنسوا قبل البدء أن تصلّوا وتسلّموا على رسول الله ﷺ، حتى يفتح علينا الله، ويبارك لنا في وقتنا وفهمنا .



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Antimuscarinic Agents

- Antimuscarinic agents **block M3 muscarinic receptors** on airway smooth muscle. **Stimulation of these receptors normally causes bronchoconstriction; however, their blockade prevents this effect, resulting in bronchodilation.** They are **classified into:**

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

- They are derivatives of **atropine**/**acetylcholine**.
- Block airway smooth muscle contraction and the increase of mucus secretion produced by acetylcholine, through actions on M_3 muscarinic receptors.

Antimuscarinic Agents

- They are ionized quaternary ammonium compounds (+), Not suitable for oral administration.
- Usually administered by inhalation, and the action is confined to the airway.
- Do not cross the blood brain barrier (No effect on CNS).
- They do **not** inhibit **ciliary movement**, in contrast to atropine, thereby allowing mucus to be expelled outward toward the pharynx, preventing mucus retention and bronchial obstruction, and avoiding accumulation of secretions.

Antimuscarinic Agents

- The magnitude of action is proportional to the contribution of parasympathetic stimulation to airway smooth muscle tone in asthmatic patients.
- Antimuscarinic agents are **not physiological bronchodilators** because they produce bronchodilation only by blocking parasympathetic-mediated bronchoconstriction. In contrast, β_2-agonists and theophylline are **physiological bronchodilators**, as they directly induce bronchodilation. This is considered a drawback of antimuscarinic agents, as they are generally **less effective** when used alone compared with physiological bronchodilators.

Antimuscarinic Agents: Therapeutic Uses

- Mainly used for treatment of COPD only in cases where there is a reversible obstruction component.
  - However, they are **not useful in cases of irreversible mechanical obstruction**, because this obstruction is **caused by damage to the bronchi. As a result of this damage, parasympathetic cholinergic nerves in the bronchi become exposed**, and **this exposure produces a certain degree of reversibility in the airway obstruction.** Therefore, **antimuscarinic drugs can improve the reversible component of the obstruction**, but **they cannot treat the irreversible mechanical damage**. Do your own research.
- Can be used in bronchial asthma, but not as monotherapy, and can be combined with other drugs.

Antimuscarinic Agents: Adverse Reactions

- Dry mouth occurs mainly because **part of the inhaled dose is deposited in the mouth before reaching the airways**. This **local exposure blocks muscarinic receptors in the oral mucosa**, leading to dryness. This effect can be reduced by using a **spacer** to decrease oropharyngeal deposition, by **dose reduction**, and **by rinsing the mouth after inhalation**, which helps minimize dry mouth.
- Anticholinergic use may be associated with increased risk of **dementia** with advancing age (?).

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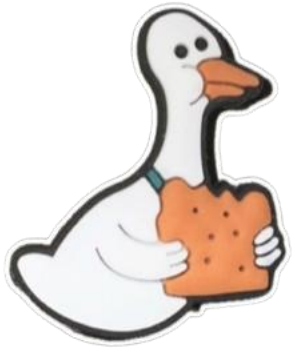
Modulators of Airway inflammation

1. Inhaled corticosteroids (Most Important).
2. Mast cell stabilizers.
3. Leukotriene pathway inhibitors.
4. Monoclonal Antibodies.



Pharmacological Modulators of Airway Inflammation

- Mast-cell Stabilizers:
  - They prevent degranulation of mast cells and the release of inflammatory and bronchoconstrictor mediators, and in this way help prevent bronchial asthma. These drugs were mainly used for prophylaxis, but they are no longer popular, because inhaled corticosteroids are more effective in preventing asthma symptoms and attacks. Therefore, mast-cell stabilizers are not considered first-line treatment.
- Leukotriene-pathway Inhibitors:
  - Leukotriene-pathway inhibitors act on leukotrienes involved in asthma, where **leukotrienes C_4 and D_4** cause **bronchoconstriction**, while **leukotriene B_4** attracts inflammatory cells and contributes to airway inflammation. When these drugs were developed, there was expectation of targeting a specific pathogenic pathway, but asthma is mediated by multiple substances, including histamine, prostaglandins, interleukins, and other mediators.

Pharmacological Modulators of Airway Inflammation

- Therefore, their clinical effectiveness was less than expected, and they are **not** considered first-line drugs. They may be used in selected cases as **add-on therapy**, but not as monotherapy.

- Monoclonal Antibodies:
  - Monoclonal antibodies are directed against mediators such as **interleukins** and **IgE**, and some of them are already available. They are specialized treatments with **specific indications**, including patients who are **resistant** to standard therapy.
  - The patient must have **allergic** asthma, as non-allergic asthma does not respond to this type of therapy. In addition, the presence of significant **eosinophilia**, meaning a high number of eosinophils in the blood, supports their use. Under these conditions, monoclonal antibodies can be considered.

Corticosteroids

- Inhalation is a major breakthrough in asthma therapy: Beclomethasone dipropionate, Triamcinolone acetonide, Budesonide, Flunisolide, Fluticasone
- **Systemic:** Prednisone PO, Methylprednisolone IV
  - Systemic corticosteroids are used only in one indication: **acute severe asthma** (status asthmaticus or severe acute exacerbation not adequately controlled with inhaled therapy). Doctor did not mention it. 
- **Corticosteroids** in combination with **β_2-agonists** are **first-line therapy** of **bronchial asthma**.
  - β_2-agonists are used to correct the **early asthmatic response** because they produce rapid bronchodilation.
  - Inhaled corticosteroids are **not bronchodilators**; they are **anti-inflammatory drugs** that reduce airway inflammation, so they prevent the **late asthmatic response**.

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Inhaled Corticosteroids

- **Most important** action is inhibition of infiltration of asthmatic airways by lymphocytes, eosinophiles, neutrophils and mast cells. (Anti-inflammatory effect)
- Inhibit production of pro-inflammatory cytokines.
- Inhibit phospholipase A_2 and thus the synthesis of arachidonic acid metabolites (PGs & LTs).
- May inhibit IgE synthesis(?!)
  - Corticosteroids exert **general immunosuppressive** effects on immune cells. However, their effect on antibody production, including IgE, is relatively **weak** compared with their other actions. At the **low** doses typically used in bronchial asthma, inhibition of IgE synthesis does not play a major role in their mechanism of action. At **higher** concentrations, corticosteroids can reduce IgE production, which becomes an additional, secondary therapeutic effect.

Inhaled Corticosteroids

- Action starts after several hours.
- Corticosteroids act mainly through **intracellular receptors**. Most of their effects are mediated by **nuclear receptors that regulate gene transcription**, followed by **mRNA translation and protein synthesis**. After these proteins are formed, they undergo **post-synthetic modification** and then move to their **sites of action**. Therefore, these **genomic effects require time**, ranging from **hours to several days**, depending on the protein involved.
- However, some pharmacologic actions of corticosteroids **occur more rapidly** and **cannot be explained by gene transcription alone**. These faster effects are attributed to **membrane-associated corticosteroid receptors located on the intracellular side of the cell membrane**.
- Thus, corticosteroids can bind **intracellular nuclear receptors**, producing **slow effects**, as well as **membrane receptors**, producing **relatively fast effects**.

Inhaled Corticosteroids

- Do **not** relax airway smooth muscle but **reduce** bronchial hyper-reactivity[a] (by prolonged therapy), reduce asthma exacerbations if used regularly, and can restore the effectiveness of β_2-agonists[b].
- Do **not** relief the acute episode.
- Improve all indices of asthma control: severity of symptoms, frequency of attacks and quality of life.
  - After an acute asthma attack is treated and the patient becomes nearly symptom-free, regular use of the β_2-agonist can be discontinued and changed to "as-needed" use, taken only when symptoms or bronchoconstriction occur. However, the inhaled corticosteroid should be continued regularly at a low maintenance dose.

Mechanisms of Action of Inhaled Corticosteroids in Asthma

A. **Reduce bronchial hyperreactivity**
   - Bronchial hyperreactivity refers to the **abnormally increased airway response** of asthmatic patients to stimuli that **do not cause symptoms in non-asthmatic individuals**. Reducing hyperreactivity makes the airways **less sensitive**, so a **stronger stimulus is required** to trigger an asthmatic attack.

B. **Restore the effectiveness of β_2-agonists (reduce tolerance)**
   - Tachyphylaxis to β_2-agonists occurs due to **downregulation of β_2 receptors**. Initially, the cell **endocytoses some receptors from the cell surface**, reducing the number of available receptors. With continued exposure, this process may extend to the **gene level**, with **reduced transcription and translation**, resulting in an **overall decrease in receptor number**.
   - For this reason, when β_2-agonists are **used alone**, a **drug-free interval between doses** is important to help reverse tolerance. For example, even if a **short-acting β_2-agonist is prescribed every six hours**, the patient should **avoid repeated nighttime dosing**, allowing receptor recovery. **Corticosteroids help prevent tolerance by inducing the synthesis of new β_2 receptors.**

Inhaled Corticosteroids

- Their effect on airway obstruction may be due in part to their contraction of engorged vessels in the bronchial mucosa.
  - Inflammation of the mucosa leads to **mucosal thickening and edema**, which **narrows the airway lumen**. Corticosteroids **inhibit vascular engorgement**, thereby **reducing mucosal edema**. As a result, the airway **opens slightly**, although this **vascular effect is minor** and **not the major mechanism of corticosteroid benefit**.

Inhaled Corticosteroids: Adverse Effects

- In addition to the systemic adverse effects:

1. **Oropharyngeal candidiasis**
   - Inhaled corticosteroids cause **local immunosuppression in the mouth and oropharynx**, allowing fungi such as **Candida** to grow more easily, leading to **oropharyngeal candidiasis**. This condition **can usually be prevented by rinsing and spitting after inhalation**.
2. **Dysphonia (hoarseness of voice)** – local effect on vocal cords
   - Dysphonia is **difficult to prevent** because the drug **can still reach the vocal cords**, even **after mouth rinsing**.
3. **Suppression of the hypothalamic–pituitary–adrenal axis**
   - **Rare**, but possible with **long-term, high-dose treatment**.

Mast-cell Stabilizers

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- 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**.
- They can be **administered by inhalation or nebulization** in bronchial asthma, but **they are not considered first-line treatments**. However, **they have additional clinical uses**, such as:
  - 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** for **ophthalmic allergy**.

Leukotriene Pathway Inhibitors

- Leukotrienes are synthesized by many inflammatory cells in the airways: eosinophiles, mast cells, macrophages and basophils.
- **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**.
- These effects can be interrupted by:
  - 5-Lipoxygenase inhibitors: Zileuton.
    - Block production of LTB_4, LTC_4, LTD_4, LTE_4.
  - LTD_4 receptor antagonists: Zafirlukast, Montelukast
    - Block the receptors but not the production
- They 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 exacerbation, but less effect on the acute onset.
- Advantage: PO administration

The underlined word is hyperlinked.

Leukotriene Pathway Inhibitors

- They were originally developed because they were thought to be particularly useful in **aspirin-induced asthma**, which results from a **shift of arachidonic acid metabolism from the cyclooxygenase pathway to the lipoxygenase pathway**, leading to **increased leukotriene production**. This mechanism **also applies to other non-steroidal anti-inflammatory drugs**, not only aspirin. However, in practice, **better control is usually achieved with inhaled β_2-agonists and inhaled corticosteroids**, which are **first-line treatments**. As a result, leukotriene pathway inhibitors **offer limited additional benefit**, are **less effective than first-line therapies**, have significant toxicity, and are **rarely used** as add-on treatment; their **main practical advantage is oral 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, with its features, occurs in approximately 5-10% of patients with bronchial 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
   - Also, major depressive disorder and some antidepressant treatments may be associated with suicidal ideation

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.
- Inhibiting drug metabolism **increases blood levels of drugs administered in their active form**, but **reduces the formation of active drug** when the medication is given as a **prodrug that requires metabolic activation**.

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, basophils, mast cells, and other inflammatory cells.
- It inhibits the binding of IgE to its receptor and thus prevent mast cell degranulation.
- In allergic asthma, allergens bind to IgE that is already attached to mast cells or basophils, triggering **cell activation and degranulation**. Anti-IgE monoclonal antibodies act by **binding free IgE**, preventing its attachment to **IgE receptors** on these cells, thereby **inhibiting mast-cell activation**. For this reason, they are used in patients with allergic asthma who are **resistant to standard therapy**.

Targeted (Monoclonal Antibody) Therapy

- It lowers free plasma IgE to undetectable levels and significantly reduces the magnitude of both early and late bronchospsatic responses, including degranulation, bronchoconstriction and inflammation, to antigen challenge.
- Its most important clinical effect is reduction in the frequency and severity of asthma exacerbation, and reduction of corticosteroid requirements, since it works similarly to corticosteroids in some respects.

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.
- What is the main indication for the use of anti-IgE monoclonal antibodies in bronchial asthma?
  - Its use is restricted to patients with **moderate-to-severe asthma**, with evidence of **perennial allergic sensitization**, who **remain uncontrolled or resistant despite appropriate first-line and add-on therapies**.

Perennial Allergic Sensitization Definition

- **A long-lasting, non-seasonal allergic sensitization** that is **present throughout the year** and **not limited to specific seasons** such as spring or autumn. It is usually caused by **continuous exposure to indoor allergens**, including house dust mites, molds, damp environments, or animal dander, rather than seasonal pollens.

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Targeted (Monoclonal Antibody) Therapy: Anti IL-5 Therapy

- T_2 helper (Th2) 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.
- Asthma is classified into **allergic and non-allergic types**, and it can also be categorized into **eosinophilic and non-eosinophilic phenotypes**. Anti-interleukin-5 therapy is mainly used to treat **severe eosinophilic asthma**, as it specifically targets **eosinophil-mediated inflammation**. Therefore, **laboratory investigations**, particularly **assessment of blood eosinophil levels**, together with a **detailed history and physical examination**, are essential to correctly identify **patients suitable for this therapy**.

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.
  - **Non-humanized (murine) monoclonal antibodies** are derived from **animal sources**, such as **mice**, and therefore contain **foreign (non-human) proteins**. As a result, they can **provoke immune reactions or allergic responses** in humans. For this reason, monoclonal antibodies are **humanized** to **reduce immunogenicity** and **improve their safety** for clinical use.
- 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**.
  - Hypersensitivity reactions are **reduced with humanized anti-IgE monoclonal antibodies**; however, they are **not completely eliminated**. Even after **purification**, **very small amounts of foreign proteins** may remain, sometimes in quantities **too small to be detected by techniques such as electrophoresis**. Despite this, these **residual proteins** can still be **allergenic** and may **trigger hypersensitivity reactions** in some patients.

Targeted (Monoclonal Antibody) Therapy

- In addition, reactivation of herpes zoster has been reported in some patients who received mepolizumab.
- Reactivation of **dormant chronic infections** is a known adverse effect of **many monoclonal antibodies**. In general, monoclonal antibodies **may reactivate latent infections** such as **herpes zoster**, **tuberculosis**, and **some fungal infections**. Therefore, monoclonal antibodies are **considered to carry a potential risk** of reactivating **latent infections**, depending on their **mechanism of action**.
- An important exception exists when a particular monoclonal antibody has been **clearly shown not to cause such reactivation**. This risk is **clinically significant**, especially for infections such as **tuberculosis**, which require **prolonged and difficult treatment** once reactivated.

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**.
- 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).

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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.
- Here we start from the **thymus**, as a result of 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).

Targeted (Monoclonal Antibody) Therapy

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.

Monoclonal antibodies are most commonly administered by **subcutaneous injection**, although **intravenous infusion** is also used **for some agents**. Their use is **restricted to specific age groups** based on **safety considerations**.

PHARMACOLOGY QUIZ LECTURE 3

External Resources

رسالة من الفريق العلمي

Additional sources:

1. Dr. AM Fouda

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار، أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

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