Current Update of New Drugs for Asthma & COPD

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ข้อแนะนำการดูแลรักษาผู้ป่วยโรคปอดอุดกั้นเรื้อรัง
กันเร็จรัง พ.ศ.2560
Current Drugs for Asthma
Introduction: Asthma

- Asthma is a **chronic disease** of the airway, marked by intermittent exacerbations of acute disease (**asthma attack**) due to **bronchial smooth muscle hyperresponsiveness**

- **Symptoms:** dyspnea, wheezing, mucus production, cough (at night)

- Asthma is **both** an obstructive lung disease & an inflammatory disease
  - **Obstructive component:** bronchoconstriction
  - **Inflammatory component:** airway edema, goblet cell hyperplasia, mucus secretion, infiltration of immune & inflammatory cells (release cytokines)

- Although airway obstruction is generally **reversible**, asthma may, over time, cause “**airway remodeling**”

- Medications used to treat asthma act in one of two ways: **by relaxing bronchial smooth muscle** or **by treating inflammation**
Asthma as an inflammatory disease

Chronic asthmatic reaction

Acute asthmatic reaction

Effect of allergic response in asthma

**Acute asthmatic reaction**
- Bronchoconstriction
- Airway edema, plasma leakage
- Mucus production

**Chronic asthmatic reaction**
- Persist bronchoconstriction
- Mucus hypersecretion
- Chronic inflammation
- Airway remodeling **

Prevent airway remodeling!!

Current pharmacologic classes and agents

- **Bronchodilator**: Short-term “reliever”
- **Anti-inflammatory agent**: Long-term “controller” ⭐
### Current pharmacologic classes and agents

<table>
<thead>
<tr>
<th>Bronchodilator “Reliever”</th>
<th>Anti-inflammatory agent “Controller”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled short-acting β₂-agonist (SABA)</strong></td>
<td><strong>Inhaled corticosteroid (ICS)</strong></td>
</tr>
<tr>
<td>– Salbutamol, terbutaline</td>
<td>– Budesonide, fluticasone propionate, beclomethasone dipropionate, mometasone</td>
</tr>
<tr>
<td><strong>Inhaled long-acting β₂-agonist (LABA)</strong></td>
<td></td>
</tr>
<tr>
<td>– Salmeterol, formoterol</td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled short-acting muscarinic antagonist (SAMA)</strong></td>
<td><strong>Antileukotrienes</strong></td>
</tr>
<tr>
<td>– Ipratropium bromide</td>
<td>– Montelukast, pranlukast, zafirlukast</td>
</tr>
<tr>
<td><strong>Inhaled long-acting muscarinic antagonist (LAMA)</strong></td>
<td><strong>Cromolyn</strong></td>
</tr>
<tr>
<td>– Tiotropium bromide</td>
<td>– Sodium cromoglycate, nedocromil sodium</td>
</tr>
<tr>
<td><strong>Methylxanthine</strong></td>
<td>**Anti-immunoglobulin E *****</td>
</tr>
<tr>
<td>– Slow-release theophylline, aminophylline</td>
<td>– Omalizumab</td>
</tr>
<tr>
<td>**Anti-IL5 (for eosinophilic asthma) *****</td>
<td>**Anti-IL4 *****</td>
</tr>
<tr>
<td>– Mepolizumab (anti-IL5), Reslizumab (anti-IL5), Benralizumab (anti-IL5Ra)</td>
<td>– Dupilumab</td>
</tr>
</tbody>
</table>
Stepwise approach to control asthma symptoms by GINA 2019

Box 3-5A
Adults & adolescents 12+ years

**Personalized asthma management:**
Assess, Adjust, Review response

**Asthma medication options:**
Adjust treatment up and down for individual patient needs

**PREFERRED CONTROLLER**
to prevent exacerbations and control symptoms

**PREFERRED RELIEVER**
Other reliever option

### STEP 1
**As-needed low dose ICS-formoterol**
- Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *
- Low dose ICS taken whenever SABA is taken †

### STEP 2
- **STEP 2**
  - Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †

### STEP 3
- **STEP 3**
  - Medium dose ICS, or low dose ICS+LTRA #

### STEP 4
- **STEP 4**
  - Refer for phenotypic assessment + add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
  - Medium dose ICS, or add-on tiotropium, or add-on ITRA #

### STEP 5
- **STEP 5**
  - High dose ICS-LABA
  - Add low dose OCS, but consider side-effects

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• **Step 1** is for patients with symptoms less than twice a month, and with no exacerbation risk factors

• For safety, GINA no longer recommends SABA-only treatment for Step 1
  – Frequent or regular use of SABA is associated with adverse effects
    • β-receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response
    • Increased allergic response, increased eosinophilic airway inflammation
  – SABA-only treatment increases risk of severe exacerbations
  – Adding any ICS -> reduces risk

• All asthma should receive regular low dose ICS-containing controller treatment, to reduce the risk of serious exacerbations => As-needed low dose ICS-formoterol (off-label)
  – With risk reduction strategy, e.g. statins, anti-hypertensives
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Time to First Exacerbation (Severe)

How common is severe asthma?

Box 1. What proportion of adults have difficult-to-treat or severe asthma?

- 24% 
  GINA Step 4-5 treatment

- 17% 
  difficult-to-treat asthma
  = GINA Step 4-5 treatment + poor symptom control

- 3.7% 
  severe asthma
  = GINA Step 4-5 treatment + poor symptom control + good adherence and inhaler technique

These data are from a Dutch population survey of people ≥18 years with asthma²

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Changes in GINA 2019 – Severe asthma

**Anti-IgE**

Is the patient eligible for anti-IgE for severe allergic asthma?
- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

**Anti-IL5 / Anti-IL5R**

Is the patient eligible for anti-IL5/anti-IL5R for severe eosinophilic asthma?
- Exacerbations in last year
- Blood eosinophils ≥300/μl

**Anti-IL4R**

Is the patient eligible for anti-IL4R for severe eosinophilic asthma?
- Exacerbations in last year
- Blood eosinophils ≥150/μl or FeNO ≥25 ppb

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**What factors may predict good asthma response to anti-IgE?**
- Blood eosinophils ≥260/μl
- FeNO ≥20 ppb
- Allergen-driven symptoms
- Childhood-onset asthma

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**What factors may predict good asthma response to anti-IL5/5R?**
- Higher blood eosinophils
- More exacerbations in previous year
- Adult-onset of asthma
- Nasal polyposis

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**What factors may predict good asthma response to anti-IL4R?**
- Higher blood eosinophils
- Higher FeNO
- Anti-IL4R may also be used to treat
- Moderate/severe atopic dermatitis
- Nasal polyposis

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**Extend trial to 6-12 months**

**Choose one if eligible; trial for at least 4 months and assess response**

**STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible

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New Biological Drugs for Uncontrolled Asthma
Biological drugs (ยาชีววัตถุ)

- omab
- ximab
- zumab
- umab

- Fab region
- Fc region

- Light chain
- Heavy chain

- Effector response
- Immune response

- Murine (0% human)
- Chimeric (65% human)
- Humanized (> 90% human)
- Fully Human (100% human)

- suffix -omab -ximab -zumab -umab

High Potential for immunogenicity Low
Current biological therapies for asthma

Most biologics focus on IgE and $T_H^2$ cytokines: IL-4, IL-5, and IL-13-based therapies

- **Anti-IgE**: Omalizumab
- **Antagonism of $T_H^2$ cytokines**
  - IL-5: Mepolizumab, Reslizumab, Benralizumab
  - IL-4: Dupilumab
  - IL-13: Lebrikizumab, Tralokinumab

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Ann Allergy Asthma Immunol
2014;112: 108-115.
IgE-targeted therapies

Omalizumab
Omalizumab (Xolair®)

*Humanized mAb binds directly to free IgE*

- FDA Approval: *Xolair®* (Genentech & Novartis, 2003): For the treatment of moderate to severe persistent allergic asthma incomplete controlled with ICS (> 6 years)
- Total serum IgE level: 30-700 IU/mL (> 12 years), 30-1300 IU/mL (6-11 years) or 30-1500 IU/mL (EU)
- Dose: 0.016 mg/kg per IU of IgE in a 4-week period, Sc

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**Total IgE levels and high-affinity IgE receptor expression is increased in asthma**

*Nat Rev Immunol 2008; 8:218-30*
EXTRA & INNOVATE Study:
Omalizumab reduced rate of future asthma exacerbations and improved lung function

IL-5-targeted therapies

- Mepolizumab
- Reslizumab
- Benralizumab
Asthma Phenotyping

- **Asthma phenotypes:**
  - $T_H^2$ (or $T_H^2$ High)
  - $T_H^1$ (or $T_H^2$ Low)

- Most asthma therapies are **non-specific** so clinical applications are limited

- The exception is broad division of patients based on presence or absence of **significant eosinophilia**

- The current targeted therapies are directed at **eosinophilic phenotype**

- Most asthmas are associated with $T_H^2$ cell-dependent production of IgE and recruitment of eosinophils, mast cells and basophils
Asthma can be divided into $T_{H}2$ and $T_{H}1$ phenotypes.
# Characteristics of asthma phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Features</th>
<th>Pathobiology &amp; Biomarker</th>
<th>Response to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic asthma</strong></td>
<td>Early onset</td>
<td>Specific IgE, $T_H^2$ cytokine</td>
<td>Corticosteroid-responsive, $T_H^2$-targeted</td>
</tr>
<tr>
<td></td>
<td>Mild-Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophilic asthma</strong></td>
<td>Later onset</td>
<td>Eosinophilia, IL-5</td>
<td>Anti-IL-5 antibody, Cysteinyll leukotriene modifier, Corticosteroid-refractory</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exercise-induced asthma (EIA)</strong></td>
<td>Early onset</td>
<td>Mast-cell activation, $T_H^2$ cytokine, Cysteinyll leukotriene</td>
<td>Cysteinyll leukotriene modifier, $\beta_2$-agonist, Anti-IL-9 antibody</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>(Intermittent with exercise)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Intermittent with exercise)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Obesity-associated asthma</strong></td>
<td>Very late onset</td>
<td>No $T_H^2$ cytokine, Oxidative stress</td>
<td>Weight loss, Antioxidant, Hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophilic asthma</strong></td>
<td>Very late onset</td>
<td>Neutrophilia, $T_H^17$ cytokines, IL-8</td>
<td>Macrolide (possible)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Eosinophils & IL-5 in asthma

- Eosinophils are equipped with **cell-surface receptors** produce specific **cytokines and chemokines**
- **IL-5** is the most specific cytokine in eosinophil regulatory pathways which are critical effectors to asthma
- **Eosinophils** are major source of **IL-5** and highly express **IL-5Ra** on surface
- **Anti-IL-5** (mepolizumab and reslizumab) & **anti-IL-5Ra** (benralizumab) are safe and efficacious in adult patients with eosinophilic asthma
Eosinophils interact with several cells of immune system

- T<sub>H2</sub> cell recruitment
- Priming
- Antigen-specific interactions
  - ↑ Proliferation and cytokine production
- B cell
  - ↑ IgM production
- T<sub>H2</sub> cell
- Neutrophil
  - ↑ Superoxide
  - ↑ IL-8
  - ↑ CR3
- B cell
  - MBP, ECP, EPX, NGF
- Macrophage
  - Maintains alternatively activated macrophages in adipose tissue
- Mast cell
  - Histamine release
  - ↑ Survival
- Bone marrow plasmablast
  - ↑ Survival
- DC
  - ↑ Maturation
- Eosinophil
  - MHC class II
  - Co-stimulatory molecules
  - IL-4, IL-13
  - EDN
  - CpG DNA
- CCL17, CCL22
- APRIL, IL-6
Targeting IL-5 or IL-5Ra is an approach for eosinophilic asthma

Natural killer (NK) cell ADCC: antibody-dependent cellular cytotoxicity

Eosinophil

- Bone marrow differentiation and maturation
- Increased cell migration
- Increased release of granule proteins
- Increased respiratory burst

Eosinophil degranulation:
- ECP
- MBP
- EPX
- EDN

IL-3, IL-5 GM-CSF

Enhanced Functional Activity

Hightened responsiveness to mediators

Reslizumab
Mepolizumab

IL-5

IL-5Rα

ADCC: antibody-dependent cellular cytotoxicity
**Mepolizumab (Nucala®)**  
*Humanized IgG1 mAb against IL-5*

- **FDA Approval:** Nucala® (GSK, Nov 2015): For the treatment of severe eosinophilic asthma unresponsive to GINA step 4 or 5 therapy (≥ 12 years, US or ≥ 6 years, US)
- **Blood eosinophils ≥ 150 cells/μl during optimization phase OR ≥ 300 cells/μl in the past 12 months (No strict eosinophil cutoff)**
- **Dose:** 100 mg SC q 4 wk

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Dose</th>
<th>Outcome</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| Chupp et al. MUSCA study 2017 | Severe eosinophilic asthma with high ICS N=551 | 100 mg Sc Q4wk, 20 wk        | ↑ FEV1 (176 mL)  
↓ Exacerbations  
Improve quality of life | Headache, URI, nasopharyngitis, injection-site reaction |
| Ortega et al. MENSA study 2014 | Severe eosinophilic asthma with high ICS N=576 | 75mg IV or 100 mg Sc Q4wk, 32 wk | ↓ Exacerbations (47% IV, 53% Sc)  
↓ Eosinophil (sputum, blood)  
↑ FEV1 (100 mL IV, 98 mL Sc) | Headache, URI, nasopharyngitis, injection-site reaction |
| Bel et al. SIRIUS study 2014 | Eosinophilic asthma with oral steroid N=135     | 100 mg Sc Q4wk, 20 wk        | ↓ Exacerbations (32%)  
Improve ACQ scores | Headache, nasopharyngitis, injection-site reaction |
| Pavord et al. DREAM study 2012 | Eosinophilic asthma with high ICS or oral steroid N=621 | 75, 250, 750 mg IV Q4wk, 13 wk | ↓ Exacerbations (48% 75 mg , 39% 250 mg )  
↓ Eosinophil (sputum, blood)  
↔ FEV1, ↔ ACQ, AQLQ scores | Headache, nasopharyngitis, injection-site reaction |
MENSA Study:
Mepolizumab reduced asthma exacerbations and improved asthma control in uncontrolled eosinophilic asthma

Asthma Exacerbations

Reslizumab (Cinqair®)
Humanized IgG4 mAb against IL-5

- FDA Approval: **Cinqair® (Teva Pharmaceuticals, March 2016):** For the treatment of severe eosinophilic asthma unresponsive to GINA step 4 or 5 therapy (> 18 years)
- Blood eosinophil > 400 cells/μL at initiation of therapy (No strict eosinophil cutoff)
- Does: 3 mg/kg q 4 wk IV infusion over 20-50 min

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Dose</th>
<th>Outcome</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castro et al. 2015</td>
<td>Severe eosinophilic asthma with high ICS N=953</td>
<td>3 mg/kg IV q4wk, 1 year</td>
<td>↓ Exacerbations</td>
<td>URI, nasopharyngitis, injection-site reaction</td>
</tr>
<tr>
<td>Castro et al. 2011</td>
<td>Severe eosinophilic asthma with high ICS N=106</td>
<td>3 mg/kg IV q4wk, 12 wk</td>
<td>↓ Exacerbations, ↓ Eosinophil (sputum, blood) Improve ACQ ↑ FEV1</td>
<td>URI, nasopharyngitis, injection-site reaction</td>
</tr>
<tr>
<td>Kips et al. 2003</td>
<td>Severe persistent asthma with high ICS or oral steroid N=28</td>
<td>0.03–1 mg/kg IV, Once</td>
<td>↓ Eosinophil (blood)</td>
<td>-</td>
</tr>
</tbody>
</table>
Benralizumab (Fasenra®)
*Humanized mAb targeting alpha-chain of IL-5 receptor*

- **FDA Approval:** Fasenra® (AstraZeneca, March 2017): For add-on maintenance treatment of severe eosinophilic asthma unresponsive to GINA step 4 or 5 (≥ 12 years)
- **Blood eosinophil ≥ 300 cells/µL** (No strict eosinophil cutoff)
- **Does:** 30 mg Sc, q 4 wk for the first 3 doses, then q 8 wk

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Dose</th>
<th>Outcome</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleecker et al. SIROCCO study 2016</td>
<td>Severe eosinophilic asthma with high ICS and LABA N=1,205</td>
<td>30 mg Sc q4wk or q8wk, 48 wk</td>
<td>↓ Exacerbations (45% q4wk, 51% q8wk) ↑ FEV1 (106 mL q4wk, 159 mL q8wk) Improve HRQoL</td>
<td>Nasopharyngitis, injection-site reaction</td>
</tr>
<tr>
<td>FitzGerald et al. CALIMA study 2016</td>
<td>Severe eosinophilic asthma with high ICS and LABA N=1,306</td>
<td>30 mg Sc q4wk or q8wk, 56 wk</td>
<td>↓ Exacerbations (36% q4wk, 28% q8wk) ↑ FEV1 (125 mL q4wk, 116 mL q8wk) Improve HRQoL</td>
<td>Nasopharyngitis, injection-site reaction</td>
</tr>
<tr>
<td>Nowak et al. 2015</td>
<td>Uncontrolled asthma after acute attack N=74</td>
<td>0.3 mg/kg IV, Once</td>
<td>↓ Exacerbations ↓ Eosinophil (blood) ↔ FEV1, ↔ HRQoL</td>
<td>Headache, cough, bronchitis</td>
</tr>
<tr>
<td>Castro et al. 2014</td>
<td>Eosinophilic asthma N=609</td>
<td>2, 20, 200 mg Sc q4wk for 3 wk, then q8wk for 1 year</td>
<td>↓ Exacerbations ↑ FEV1 Improve HRQoL</td>
<td>Nasopharyngitis injection-site reaction</td>
</tr>
</tbody>
</table>
IL-4-targeted therapies

*Dupiluminab*
Dupilumab (Dupixent®)

*Whole human mAb against IL-4Rα*

- **FDA Approval:** *Dupixent®* (Regeneron & Sanofi Genzyme, Oct 2018): For add-on maintenance therapy in patients with moderate-to-severe asthma with an eosinophilic phenotype or with corticosteroid-dependent asthma (>12 years)

- **Mechanism:** Binds to IL-4 receptor alpha -> blocks signaling of IL-4 and IL-13 and decreases markers of Type 2 inflammation, including
  - ↓ Total & allergen-specific IgE
  - ↓ FeNO (a marker of lung inflammation)
  - ↓ Eosinophilic inflammation

- **Dose:** 400-600 mg SC loading dose followed by 200-300 mg Sc q2wk
 Dupilumab: Mechanism of action

 Dupilumab: Binds to IL-4 receptor alpha; blocks signaling of IL-4 and IL-13

VENTURE study:
Dupilumab decreased OCS dose and improve lung function

Percentage reduction in oral glucocorticoid dose

FEV1 Change from Baseline

Summary: Biological Drugs for Uncontrolled Asthma

- Accurate characterization of *asthma phenotypes* is essential for development and implementation of biological treatment.
- Targeted therapies against IgE, IL-5 and IL-4 seem safe and promising in short- and medium-term treatment of adult patients with uncontrolled asthma.
- Safety and efficacy studies of cytokine-specific monoclonal antibody therapies in children are still needed.
- The cost-effectiveness and adverse events associated with the use of each monoclonal antibody should be considered (clinical trials).
- Identification of *specific biomarkers*, in addition to sputum and blood eosinophilia, will allow a more selective identification of patients responsive to these treatments.
Current Drugs for COPD
Introduction: COPD

• COPD is a **progressive disease** that is characterized by a **persistent blockage of airflow from the lungs** (not fully reversible)

• COPD: **Chronic bronchitis & Emphysema**

• **Cause**: Long-term exposure to lung irritants (**cigarette smoke**)

• **Main symptoms**: breathlessness, abnormal sputum, chronic cough, daily activities become difficult (gradually worsens)

• **Treatment**: COPD has no cure (**Quitting smoking!**) (Others: medicines, vaccines, pulmonary rehabilitation, oxygen therapy)

• **Diagnosis**: Spirometry

  (post-bronchodilator FEV1/FVC < 0.70)

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![COPD Prevalence by Sex and Age](image-url)
Therapeutic options: Key points

- **Smoking cessation*** (5 A’s: ask, advise, assess, assist, arrange)
- Appropriate *pharmacologic therapy* can reduce COPD symptoms, reduce frequency and severity of exacerbations, improve exercise tolerance
- Each pharmacologic treatment regimen *should be individualized*
- *Inhaler technique* needs to be assessed regularly
- *Influenza vaccination* reduce serious illness (such as lower respiratory tract infections) and death in COPD patients
- *Pneumococcal vaccinations (PCV13 & PPSV23)* are recommended for all patients ≥ 65 years of age
- *Pulmonary rehabilitation* improves symptoms, quality of life, and physical and emotional participation in everyday activities
Pharmacologic treatment algorithms for stable COPD

**INITIAL PHARMACOLOGICAL TREATMENT**

- **Group A**: 0 or 1 moderate exacerbations (not leading to hospitalization)
  - A Bronchodilator
  - mMRC 0-1 CAT < 10

- **Group C**: ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization
  - LAMA

- **Group D**: LAMA or LAMA + LABA* or ICS + LABA**
  - *Consider if highly symptomatic (e.g. CAT > 20)
  - **Consider if eos ≥ 300

- **Group B**: A Long Acting Bronchodilator (LABA or LAMA)
  - mMRC ≥ 2 CAT ≥ 10

**FIGURE 4.1**

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New pharmacotherapies for COPD

**LAMA monotherapy**

- **Aclidinium**
  - Faster onset of action (compared to tiotropium)
  - Good night-time FEV1
  - BID dosing

- **Glycopyrronium**
  - Rapid onset
  - Good safety profile (less antimuscarinic & cardiac side effects)

- **Umeclidinium**
  - Minimal antimuscarinic side effects
  - Combined with vilanterol

**LABA monotherapy**

*Ultra-long-acting β₂ agonist*

- **Indacaterol**
  - Improved cardiovascular safety profile & lung function

- **Vilanterol**
  - Ultra-long-acting β₂ agonist
  - Combined with fluticasone furoate

- **Olodaterol**
  - Ultra-long-acting β₂ agonist

- **Abediterol**
  - Better lung function (compared to indacaterol)
New pharmacotherapies for COPD

LABA-LAMA combination therapy

- **Umeclidinium & Vilanterol**
  - Low adverse events
  - First LAMA-LABA approved by US FDA for maintenance treatment
- **Glycopyrronium & Indacaterol**
  - Low adverse events
  - Better FEV1 and SGRQ
- **Tiotropium & Olodaterol**
  - Improved SGRQ score
  - Low adverse events
- **Aclidinium & Formoterol**
  - Improved FEV1
- **Glycopyrrolate & Formoterol**
  - Improved FEV1

LABA-ICS combination therapy

- **Vilanterol & Fluticasone**
  - Once-daily
  - Increased risk of pneumonia (compared to vilanterol alone)
- **Indacaterol & Mometasone**
  - Studied in persistent asthma
- **Formoterol & Ciclesonide**
  - Similar to fluticasone propionate/salmeterol
- **Formoterol & Fluticasone**
  - Rapid bronchodilator effect than fluticasone propionate/salmeterol
  - Approved for asthma, Phase III for moderate to severe COPD
Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Time to First Exacerbation