Three’s Company - The role of triple therapy in chronic obstructive pulmonary disease (COPD)

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Learning Objectives

By the end of this session, the learner should be able to...

• **Identify** COPD patients who are potential candidates for triple therapy
• **Compare** the use of “fixed” triple therapy with “open” triple therapy
• **Explain** the role of using inhaled corticosteroids (ICS) in a COPD patient
Background

- COPD affects approximately 64 million people worldwide and is the 3rd leading cause of death.
- Chronic inflammatory disease with persistent airflow limitation
## Classification of COPD

**Figure 1: Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV1) in patients with FEV1/FVC < 0.70**

<table>
<thead>
<tr>
<th>GOLD 1</th>
<th>Mild</th>
<th>FEV1 &gt; 80% of predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>FEV1 50-79% of predicted</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>FEV1 30-49% of predicted</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very Severe</td>
<td>FEV1 &lt; 30% of predicted</td>
</tr>
</tbody>
</table>

Global Initiative for Chronic Obstructive Lung Disease. 2018
## Classification of COPD

### Exacerbation History

<table>
<thead>
<tr>
<th>&gt; 2 or &gt; 1 leading to hospitalization</th>
<th>GROUP C</th>
<th>GROUP D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1 (not leading to hospitalization)</td>
<td>GROUP A</td>
<td>GROUP B</td>
</tr>
</tbody>
</table>

### Symptom Severity

- mMRC 0-1
- CAT < 10

- mMRC > 2
- CAT ≥ 10

Global Initiative for Chronic Obstructive Lung Disease. 2018
Test your Knowledge

• Patient HT is a 69-year-old male who presents to your clinic. His most recent pulmonary tests show an FEV1/FVC: 47%, FEV1: 29% of expected, 2 exacerbations in previous year, 1 requiring hospitalization. The patient reports that he had to stop for breath several times to enter your office from the parking lot today (mMRC 3).

• How would you classify this patient’s COPD?
  A. GOLD 1, Group A
  B. GOLD 2, Group B
  C. GOLD 3, Group C
  D. GOLD 4, Group D
Test your Knowledge

• Patient HT is a 69-year-old male who presents to your clinic. His most recent pulmonary tests show an FEV1/FVC: 47%, FEV1: 29% of expected, 2 exacerbations in previous year, 1 requiring hospitalization. The patient reports that he had to stop for breath several times to enter your office from the parking lot today (mMRC 3).

• How would you classify this patient’s COPD?
  A. GOLD 1, Group A
  B. GOLD 2, Group B
  C. GOLD 3, Group C
  D. GOLD 4, Group D
Pharmacologic Options

- Beta Agonists
  - Short acting (SABA)
  - Long acting (LABA)
- Muscarinic Antagonist
  - Short acting (SAMA)
  - Long acting (LAMA)
- Inhaled Corticosteroids
Group A

Short acting bronchodilator (SABA/SAMA) as needed

Group B

Long-acting bronchodilator (LAMA/LABA) LABA + LAMA

Group C

LAMA LAMA + LABA LABA + ICS

Group D

LAMA + LABA LABA + ICS LAMA + LABA + ICS
The 3 major questions...

1. Which patients will benefit the most from triple therapy?
2. Is “fixed” triple therapy better than “open” triple therapy?
3. Which patients are at an increased risk for pneumonia?
What we already know...

1. Which patients will benefit the most from triple therapy?
2. Is “fixed” triple therapy better than “open” triple therapy?
3. Which patients are at an increased risk for pneumonia?
TRILOGY:
Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease

Enrollment: March 2014 - January 2016
Release date: September 2016
159 sites across 14 countries

TRILOGY TRIAL

Treatment Arms
• Beclomethasone + formoterol + glycopyrrolate (ICS/LABA/LAMA)
• Beclomethasone + formoterol (ICS/LABA)

Primary Outcome(s)
• Change in pre-dose FEV1 and 2-hour post-dose FEV1 at 26 weeks

Select Secondary Outcome(s)
• COPD exacerbation frequency over 52 weeks

TRILOGY Trial

Inclusion Criteria

• Age 40+
• Prebronchodilator FEV1 <60% predicted
• 1+ moderate/severe exacerbation within 12 months
• Current or former smokers (10 pack-year history)
• CAT > 10

Exclusion Criteria

• Alpha-1 antitrypsin deficiency
• Asthma, allergic rhinitis or non-COPD pulmonary condition
• COPD exacerbation within last 4 weeks
• Requiring long term oxygen
• Already on ICS/LABA/LAMA regimen

VETERANS HEALTH ADMINISTRATION
**Baseline Characteristics**

- 1181 patients completed study
  - 602 in ICS/LABA/LAMA
  - 579 in ICS/LABA
- Average age: 63 years old
- **Average FEV1: ~36% of predicted – severe airflow limitation**
- **Average CAT score 20.8 – highly symptomatic**
- 47% active smokers
- **1.2 exacerbations in the previous year**
- COPD medication at study entry
  - ICS/LABA or ICS/LAMA – 75%
  - LABA/LAMA – 14%
  - LAMA – 11%
TRILOGY Trial

**Pre-dose FEV1 at 26 weeks**
- Triple therapy increased FEV1 82 ml vs ICS/LABA, which increased FEV1 by 1 ml
- Adjusted mean difference: 81 ml (p<0.001, CI 52-109 ml)

**Post-dose FEV1 at 26 weeks**
- Triple therapy increased FEV1 261 ml vs ICS/LABA, which increased FEV1 by 145 ml
- Adjusted mean difference: 117 ml (p<0.001, CI 86-147 ml)
Trilogy Trial

Strengths
• 2-week run-in with dual therapy
• Excluded patients who were previously on triple therapy

Limitations
• Benefit of LAMA/LABA not examined
• Exacerbation history not defined well
• Use of appropriate patient population questionable

Triple therapy increased both pre- and post-dose FEV1 and decreased exacerbation rate compared to ICS/LABA in patients with severe airflow limitation and history of exacerbations.
IMPACT:
Once-Daily Single-Inhaler Triple vs Dual-Therapy in Patients with COPD

Enrollment: June 2014 - July 2017
Release date: May 2018
37 countries

VETERANS HEALTH ADMINISTRATION
IMPACT Trial

Treatment Arms
• Fluticasone Furoate + Umeclidinium + Vilanterol (ICS/LAMA/LABA)
• Fluticasone + Vilanterol (ICS/LABA)
• Umeclidinium + Vilanterol (LAMA/LABA)

Primary Outcome(s)
• Moderate-severe exacerbation rate over 52 weeks

Select Secondary Outcomes
• Change in FEV1
• Change in St Georges Respiratory Questionnaire (SGRQ)

**IMPACT Trial**

**Inclusion Criteria**
- Age 40+
- Current or former smokers
- CAT Score > 10
- FEV1 <50% of expected + 1 mod-severe exacerbation in previous year or
- FEV1 50-70% of expected + 2+ moderate exacerbations in previous year

**Exclusion Criteria**
- Alpha-1 antitrypsin deficiency
- Severe cardiac dysfunction
- Allergic rhinitis or non-COPD pulmonary condition
- Requiring long-term oxygen
- Chronic use of antibiotics or oral steroids

Baseline Characteristics

- 10,355 patients in study
  - 4151 in ICS/LABA/LAMA
  - 4134 in ICS/LABA
  - 2070 in LABA/LAMA
- Average age: 65 years old
- **Average CAT score of 20.1**
- **Average FEV1 ~45% of predicted – severe airflow limitation**
- 26%: 1 severe COPD exacerbation in previous year
- 4%: 2+ severe COPD exacerbations in previous year
- 47%: 2+ moderate COPD exacerbations in previous year
- 11%: 3+ moderate-severe exacerbations in previous year
### IMPACT Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICS/LABA/LAMA (N = 4151)</th>
<th>ICS/LABA (N = 4134)</th>
<th>LABA/LAMA (N = 2070)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod-severe exacerbations (year⁻¹)</td>
<td>0.91</td>
<td>1.07</td>
<td>1.21</td>
</tr>
<tr>
<td>Change in FEV₁ (mL)</td>
<td>94 (86, 102)</td>
<td>-3 (-12, 6)</td>
<td>40 (28, 52)</td>
</tr>
<tr>
<td>Change in SGRQ (points)</td>
<td>-5.5 (-5.9, -5.0)</td>
<td>-3.7 (-4.2, -3.2)</td>
<td>-3.7 (-4.4, -3.0)</td>
</tr>
</tbody>
</table>

Strengths
• Sample size > 10,000
• Appropriate patient population
• Considered patient’s quality of life using the SGRQ

Limitations
• 60% of patients “stepped down” to dual therapy
• Patients with a concomitant history of asthma were not excluded

Triple therapy decreased exacerbation rate and increased FEV1 and quality of life compared to ICS/LABA and LAMA/LABA in patients with severe airflow limitation and history of exacerbations.
SUNSET:
Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease

Enrollment: November 2015 - July 2017
Release date: August 2018
21 countries

SUNSET Trial

Treatment Arms
3-week run-in period of Tiotropium + Salmeterol + Fluticasone
• Tiotropium + Salmeterol + Fluticasone (LAMA/LABA/ICS)
• Indacaterol + glycopyrrolate (LABA/LAMA)

Primary Outcome(s)
• Change in FEV1 after 26 weeks of treatment
• Non-inferiority margin 50 ml

Select Secondary Outcomes
• Exacerbation rate over 26 weeks

SUNSET Trial

Inclusion Criteria
• Age 40+
• FEV1 40-80% predicted
• No more than 1 moderate/severe exacerbation within 12 months
• Current or former smokers (10 pack-year history)
• Receiving ICS/LABA/LAMA for 6+ months

Exclusion Criteria
• Alpha-1 antitrypsin deficiency
• Asthma, allergic rhinitis or non-COPD pulmonary condition
• Requiring long term oxygen
• Blood eosinophil count > 600 cells/µl

SUNSET Trial

Baseline Characteristics

- 1053 patients in study
  - 527 in ICS/LABA
  - 526 in ICS/LABA/LAMA
- Average age: 65 years old
- Average FEV1 ~56.6% of predicted – moderate airflow limitation
- 34.1% had one exacerbation in previous year
- 65% had zero exacerbations in previous year

SUNSET Trial

SUNSET Trial

Moderate or severe exacerbations
Rate ratio (95% CI): 1.08 (0.83 to 1.40)

\[ P = 0.5802 \]

Annualized rate (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indacaterol/Glycopyrronium (N = 527)</td>
<td>0.52 (0.46 to 0.58)</td>
</tr>
<tr>
<td>Tiotropium plus Salmeterol/Fluticasone (N = 526)</td>
<td>0.48 (0.42 to 0.54)</td>
</tr>
</tbody>
</table>

SUNSET Trial

A

Eosinophils (cells/μL) *

| <300 | 386 | 390 | -0.013 (-0.044 to 0.017) |
| ≥300 | 117 | 117 | -0.069 (-0.125 to -0.012) |

Difference in change in trough FEV₁ (L)

Tiotropium plus Salmeterol/Fluticasone
Better

Indacaterol/Glycopyrronium
Better

B

Eosinophils (cells/μL) *

| <300 | 401 | 406 | 0.97 (0.72 to 1.32) |
| ≥300 | 125 | 119 | 1.86 (1.06 to 3.29) |

Rate Ratio of COPD Exacerbations

Indacaterol/Glycopyrronium
Better

Tiotropium plus Salmeterol/Fluticasone
Better

Strengths

• Appropriate patient population
• Use of non-inferiority test

Limitations

• Short-term trial (6 months)
• Use of 2 different bronchodilators
• Basis of non-inferiority margin not defined

Unable to claim that de-escalation to dual therapy is non-inferior compared to triple therapy in patients with moderate airflow limitation. De-escalation may increase exacerbations in patients with high eosinophil counts.
Conclusions

**Triple Therapy**
- Class D COPD only
- Severe airflow restriction
- High eosinophil counts (300-600 cells/µL)

**Dual Therapy**
- Inappropriately escalated
- Stable on triple therapy for ≥ 6 months.
Test your Knowledge

• HT’s medication regimen includes:
  – Albuterol PRN (using 5x daily)
  – Tiotropium - Two inhalations (5 mcg) once daily
  – Salmeterol - One inhalation twice daily

• Which of the following medication regimens might you recommend for HT?
  A. Albuterol + Tiotropium
  B. Albuterol + Salmeterol
  C. Albuterol + Umeclidinium + Vilanterol
  D. Albuterol + Fluticasone + Salmeterol + Tiotropium
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  C. Albuterol + Umeclidinium + Vilanterol
  D. Albuterol + Fluticasone + Salmeterol + Tiotropium
The 3 major questions...

1. Which patients will benefit the most from triple therapy?
2. Is “fixed” triple therapy better than “open” triple therapy?
3. Which patients are at an increased risk for pneumonia?
TRINITY:
Single inhaler extra-fine triple therapy versus long-acting muscarinic antagonist therapy for COPD

Enrollment: January 2014 – March 2016
Release date: April 2017
224 sites across 15 countries

TRINITY TRIAL

Treatment Arms
• Beclomethasone + formoterol + glycopyrrolate (FIXED)
• Beclomethasone + formoterol + tiotropium (OPEN)
• Tiotropium alone

Primary Outcome(s)
• COPD moderate-severe exacerbation rate

Select Secondary Outcomes
• Change in pre-dose FEV1 at week 52

VETERANS HEALTH ADMINISTRATION

Inclusion Criteria

- Age 40-80
- FEV1 <50% predicted
- CAT > 10
- Current or former smokers (10 pack-year history)
- 1+ moderate/severe exacerbation within 12 months

Exclusion Criteria

- Alpha-1 antitrypsin deficiency
- Already receiving triple therapy
- Asthma, allergic rhinitis or Non-COPD pulmonary condition
- COPD exacerbation within last 4 weeks
- Requiring long term oxygen

## Baseline Characteristics

- 2691 patients
  - 1078 in fixed triple
  - 1075 in tiotropium
  - 538 in open triple
- Average age: 63 years old
- **Average FEV1 ~ 36.6% of predicted** – Severe airflow limitation
- **Average CAT score 21**
- 48% active smokers
- COPD medication at study entry
  - ICS/LABA or ICS/LAMA – 75%
  - LABA/LAMA – 12%
  - LAMA – 13%

TRINITY Trial

TRINITY Trial

TRINITY – Conclusions/Critique

**Strengths**

- Good follow-up period (1 year)

**Limitations**

- 90% of patients in LAMA monotherapy group de-escalated
- Ideal patient population?

When compared to multiple inhalers, “fixed” triple therapy does not appear to have an impact on FEV1 or exacerbation rate.
Test your Knowledge

• Patient OP is a 71-year-old female who presents to your clinic. Her most recent PFTs show an FEV1/FVC: 65%, FEV1: 28% of expected, and 1 exacerbation 8 months ago requiring a hospitalization. The patient is extremely upset that she is not able to run around the backyard and play tag with her grandchildren like she used to (mMRC 2).

• How would you classify this patient’s COPD?
  A. GOLD 1, Group A
  B. GOLD 2, Group B
  C. GOLD 3, Group C
  D. GOLD 4, Group D
Test your Knowledge

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  A. GOLD 1, Group A
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  C. GOLD 3, Group C
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Test your Knowledge

• OP’s medication list includes:
  – Albuterol PRN (uses 1-2 times per week)
  – Fluticasone + Vilanterol 1 inhalation twice daily

• Which of the following medication regimens might you recommend for OP?
  A. Albuterol + Tiotropium
  B. Albuterol + Salmeterol
  C. Albuterol + Umeclidinium + Vilanterol
  D. Albuterol + Fluticasone + Salmeterol + Tiotropium
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  A. Albuterol + Tiotropium
  B. Albuterol + Salmeterol
  C. Albuterol + Umeclidinium + Vilanterol
  D. Albuterol + Fluticasone + Salmeterol + Tiotropium
Have you been using your inhaler?

All the time

Are you sure you've been using it right?

Do I look like an idiot?

No...

Why don't you show me how you use it
The 3 major questions...

1. Which patients will benefit the most from triple therapy?
2. Is “fixed” triple therapy better than “open” triple therapy?
3. Which patients are at an increased risk for pneumonia?
Role of ICS in COPD

• Historically, providers hypothesized that patients with COPD and inflammation would respond to inhaled steroids similar to patients with asthma.
• Data supporting the use of ICS is limited.
• ICS use leads to adverse reactions, such as:
  – Candidiasis
  – Bruising
  – Pneumonia
TORCH:
Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Enrollment period: September 2000 – November 2005
Release date: February 2007
444 centers across 42 countries

TORCH Trial

Treatment Arms
- Fluticasone Propionate
- Salmeterol
- Fluticasone + Salmeterol
- Placebo

Primary Outcome(s)
- All-cause mortality at 3 years
- COPD-related mortality at 3 years

## TORCH Trial

<table>
<thead>
<tr>
<th>Adverse Event (%)</th>
<th>Placebo (n = 1544)</th>
<th>Salmeterol (n = 1542)</th>
<th>Fluticasone (n = 1552)</th>
<th>Combination (n = 1546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>12.3%</td>
<td>13.3%</td>
<td>18.3%</td>
<td>19.6%</td>
</tr>
</tbody>
</table>
SUMMIT:
Study to Understand Mortality and Morbidity in COPD

Enrollment period: January 2011 – July 2015
Release date: April 2016

SUMMIT Trial

Treatment Arms
- Fluticasone Furoate
- Vilanterol
- Fluticasone + vilanterol
- Placebo

Primary Outcome(s)
- Time to death from any cause

### SUMMIT Trial

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 4131)</th>
<th>Fluticasone (n = 4157)</th>
<th>Vilanterol (n = 4140)</th>
<th>Combination (n = 4140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia-related ADRs, n (%)</td>
<td>214 (5.2%)</td>
<td>228 (5.5%)</td>
<td>163 (3.9%)</td>
<td>237 (5.7%)</td>
</tr>
<tr>
<td>Pneumonia-related serious ADRs, n (%)</td>
<td>127 (3.1%)</td>
<td>146 (3.5%)</td>
<td>104 (2.5%)</td>
<td>140 (3.4%)</td>
</tr>
<tr>
<td>Pneumonia-related fatal ADRs, n (%)</td>
<td>10 (0.2%)</td>
<td>17 (0.4%)</td>
<td>5 (0.1%)</td>
<td>16 (0.4%)</td>
</tr>
</tbody>
</table>

SUMMIT trial

Fig. 2. Risk factors for Pneumonia in Placebo Arm.

Baseline FEV1 ~44%
Baseline SGRQ score 49.5
BMI ~25
Fluticasone Propionate
3 year duration

Baseline FEV1 ~59%
Baseline SGRQ score 45
BMI ~28
Fewer exacerbations
Fluticasone Furoate
15-44 month duration
Patients at higher risk of pneumonia are:

- Current smokers
- Age 55+
- BMI < 25
- Poor mMRC grade and/or severe airflow limitation (FEV1 < 50%)
- History of exacerbations and/or pneumonia
Test your knowledge

Which of these comorbidities is associated with an increased risk for pneumonia?

I. Morbid Obesity
II. Current Smoker
III. FEV1 30% of predicted

A. A. I only
B. B. I and II
C. II and III
D. I, II, and III
E. None of the above
Test your knowledge

Which of these comorbidities is associated with an increased risk for pneumonia?

I. Morbid Obesity
II. Current Smoker
III. FEV1 30% of predicted

A. A. I only
B. B. I and II
C. II and III
D. I, II, and III
E. None of the above
Conclusions

• Triple therapy

• Open vs fixed triple therapy

• Role of ICS and pneumonia
Studies in the pipeline...

**INTREPID**
Investigation of TRELEGY Effectiveness: Usual Practice Design
*December 2019*

**TRIVOLVE**
Fixed Dose Triple Therapy in Severe COPD in a Real-World Setting
*August 2019*

**AIRWISE**
Assessment In a Real World Setting of the Effect of Inhaled Steroid-based Triple Therapy Versus the Combination of Tiotropium and Olodaterol on Reducing COPD Exacerbations
*June 2020*
Thank you

• Evaluator
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• Preceptors at Central Texas Veterans Healthcare System
• Co-residents at Central Texas Veterans Healthcare System
The role of triple therapy in chronic obstructive pulmonary disease (COPD)

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October 26th, 2018