Session 2: Preventing COPD exacerbations: Talking to patients and experts about different medicines.
April 5, 2022, 12-1pm ET

Jerry Krishnan, MD, PhD
Jean Rommes, PhD
Stephen Rennard, MD
Richard Albert, MD

EXAMPLE DISCUSSION BETWEEN A PATIENT AND HER PHYSICIAN

WHY USE AZITHROMYCIN OR ROFLUMILAST
This session is being recorded.

Please use the chat box to ask questions to be answered during the Q&A.

1. **Welcome / introductions** (Krishnan, 5 min)
2. **Roleplay a decision making process** (Krishnan, Rommes, 15 min)
3. **Why use Roflumilast** (Rennard, 10 min)
4. **Why use Azithromycin** (Albert, 10 min)
5. **Roleplay closing** (Krishnan, Rommes, 5 min)
6. **Summary and Q&A** (Wise, 15 min)

Research reported in this presentation is funded through a Patient-Centered Outcomes Research Institute® (PCORI®) Award (PCS-1504-30430).

The views, statements, & opinions presented in this presentation are solely the responsibility of the author(s) and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute® (PCORI®), its Board of Governors or Methodology Committee.
Oscar win!

“DECIDING BETWEEN MEDICINES”

New Category: *Best Real World Drama*
Jean Rommes, PhD
Jerry Krishnan, MD, PhD
CLIP 1:
“DECIDING BETWEEN MEDICINES”

Jean Rommes, PhD
In the role of a patient with COPD

Jerry Krishnan, MD, PhD
In the role of a Pulmonologist at UI Health
Why use roflumilast?

Stephen Rennard, MD
My role
Executive committee member
Content expert for roflumilast

Disclosures
Clinical and basic publications
Consultant/grant support relating to roflumilast from:
- BykGulden
- Altana
- Nycomed
- Forest
- Takeda
- AstraZeneca

Employed by AstraZeneca 2015-2019, received shares as part of compensation

Equipoise with respect to the questions being addressed
In patient with chronic bronchitis...
- Is roflumilast better, worse, or similar to azithromycin in reducing the risk of hospitalization or death?
- Which medication is better tolerated?
Roflumilast for COPD Exacerbations

1. Rationale

2. Data on efficacy
   *Indicated population (chronic bronchitis)*

3. Adverse events
   *Dose up-titration*

4. Summary
Why use roflumilast? // Rationale


Change in sputum inflammatory cells

- **roflumilast** inhibits cAMP → PDE4 → degrades AMP
- **inhibits** protein phosphorylation → *Inflammation*

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Absolute Cell Numbers (% change from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cell count</td>
<td>![Bar graph with p = 0.0023] (Increase)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>![Bar graph with p = 0.0005] (Decrease)</td>
</tr>
<tr>
<td>Neutrophils</td>
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Steve 9
Registration data on exacerbations supporting approval

Two studies
Study 5: N=1537
Study 6: N=1554

Study population
COPD patients
Current/former smoker
Chronic bronchitis
FEV1 <50% predicted
At least one hospitalized exacerbation or event requiring systemic steroids

Intervention
Roflumilast (500ug vs. placebo)
52 weeks

Roflumilast improves airflow:

**Why use roflumilast? // Data on efficacy**

**Registration data on exacerbations supporting approval**

Two studies
- Study 5: N=1537
- Study 6: N=1554

**Study population**
- COPD patients
- Current/former smoker
- Chronic bronchitis
- FEV1 <50% predicted
- At least one hospitalized exacerbation or event requiring systemic steroids

**Intervention**
- Roflumilast (500ug vs. placebo)
- 52 weeks

---

**Roflumilast reduces exacerbations**

![Graph showing the reduction in exacerbations with roflumilast compared to placebo.](image)

\[ \Delta = -15\% \]

\[ \Delta = -18\% \]

\[ P=0.0278 \]

\[ P=0.0035 \]

Why use roflumilast? // Data on efficacy

Exacerbation rate:

Rationale for ‘personalized’ medicine

Two studies
Study 3: N=1327
Study 4: N=1359

Study population
COPD patients
Current/former smoker
Chronic bronchitis and/or emphysema
FEV1 <50% predicted

Intervention
Roflumilast (500ug vs. placebo)
52 weeks

**RELIANCE**

Why use roflumilast? // Data on efficacy

**Prior hospitalization: efficacy of roflumilast**

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**Table 3. Mean Rate of Moderate or Severe Exacerbations per Patient per Year at Week 52, by Subgroup**

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<td>Sex</td>
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*Martinez et al. Am J Respir Crit Care Med. 198:1268-1278, 2018*
Prior hospitalization: efficacy of roflumilast

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Martinez et al. Am J Respir Crit Care Med. 198:1268-1278, 2018

Steve 14
## Prior hospitalization: efficacy of roflumilast

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| None                              | 1,436                          | 1,452               | 0.98 (0.90–1.07)                          | 1.03 (0.95–1.12) | 0.95 (0.84–1.07) | 0.4224 |
| ≥1                                 | 703                            | 683                 | 1.06 (0.94–1.21)                          | 1.43 (1.27–1.61) | 0.74 (0.63–0.88) | 0.0005 |

*Martinez et al. Am J Respir Crit Care Med. 198:1268-1278, 2018*
## Greater than 2% on drug and drug > placebo

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*Roflumilast package insert*
## Greater than 2% on drug and drug > placebo

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## Suicide-related

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<thead>
<tr>
<th>COPD safety pool</th>
<th>placebo (N=5,491) n (%)</th>
<th>rof500 (N=5,766) n (%)</th>
<th>rof250 (N=797) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide attempt</td>
<td>–</td>
<td>2 (0.03)</td>
<td>–</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1 (0.02)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Completed suicide</td>
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*Roflumilast package insert*
### Greater than 2% on drug and drug > placebo

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<td>Completed suicide</td>
<td>–</td>
<td>1 (0.02)</td>
<td>–</td>
</tr>
</tbody>
</table>

**Contra-indications:**
Moderate to severe liver impairment (Child-Pugh B or C)

**Drug-drug interactions:**
cytochrome P450 inducers (loss of efficacy) and inhibitors of CYP3A4 and CYP1A2 (increased AEs)
Dose up-titration

Why use roflumilast? // Adverse Events

A

Probability of patients continuing study

No of patients at risk
- ROF 250 OD/ROF 500 OD: 441, 431, 411, 402, 397, 389, 376, 371, 323
- ROF 500 EOD/ROF 500 OD: 437, 423, 407, 390, 385, 379, 369, 359, 299
- ROF 500 OD: 443, 419, 382, 367, 361, 358, 352, 343, 291

Days

0 10 20 30 40 50 60 70 80

0.6 0.8 1.0

Patients with ≥1 AE of interest (%)

- All AEs of interest
- Diarrhea
- Nausea
- Headache
- Decreased appetite
- Insomnia
- Abdominal pain

OR 0.63, [95% CI 0.47–0.83], p=0.001
OR 0.78, [95% CI 0.59–1.04], p=0.09

Why use roflumilast? // Summary

**Roflumilast reduces exacerbations in patients with COPD & CB**
- No benefit in patients without CB
- Effect may be greater in more severe patients who experience hospitalization
- Modest improvement in FEV1

**Adverse events**
- Largely GI
- Diarrhea
- Nausea
- May be mitigated by dose up titration

**Cautions**
- CYP P450 inhibitors and inducers

**Contraindications**
- Moderate to severe liver impairment (Child-Pugh B or C)
Why use azithromycin?

Richard Albert, MD
The RELIANCE Study

My role
Executive committee member
Content expert for azithromycin

Disclosures
None

Equipoise with respect to the questions being addressed
In patient with chronic bronchitis...
- Is azithromycin better, worse, or similar to roflumilast in reducing the risk of hospitalization or death?
- Which medication is better tolerated?
AZITHROMYCIN FOR PREVENTION OF ACUTE EXACERBATIONS OF COPD (AECOPD)

1. Rationale
2. Data on efficacy
3. Adverse effects
4. Summary
Why use azithromycin? // Rationale

Several treatments reduce AECOPDs

- ICS
- LABA
- LAMA

Despite all three: 1.4 AECOPD/yr
Why use azithromycin? // Rationale

Mechanisms of action

- Immunomodulatory
- Anti-inflammatory
- Anti-bacterial
Macrolide antibiotics: previous studies

Seven prior studies
- Small numbers of patients (35)
- Retrospective
- Short term (3 M)
- Not blinded
- No controls

Seemungal (AJRCCM 2008)
- RCT of 109 patients
- Erythromycin 250 mg bid x 1 yr
- AECOPD decreased 35%
MACRO Study (NEJM 2011)

Study design

- RCT in 1142 patients
- Azithromycin 250 mg qd x 1 yr
- Added to usual care
  (ICS and/or LABA and/or LAMA)
Why use azithromycin? // Data on efficacy

MACRO Study (NEJM 2011)

Study design

- RCT in 1142 patients
- Azithromycin 250 mg qd x 1 yr
- Added to usual care (ICS and/or LABA and/or LAMA)
MACRO Study (NEJM 2011)

Study design

- RCT in 1142 patients
- Azithromycin 250 mg qd x 1 yr
- Added to usual care (ICS and/or LABA and/or LAMA)
MACRO Study (NEJM 2011)

Post-hoc analyses

- Unadjusted or adjusted
- Women or men
- Age < or ≥ 65 yrs
- GOLD 2, 3, 4
- Chronic bronchitis vs not
- On O2 vs not
- Smokers (HR: 0.99, 0.71-1.38) vs ex-smokers (HR: 0.65, 0.55 – 0.77)
- All inhaler combinations
Why use azithromycin? // Data on efficacy

MACRO Study (NEJM 2011)

Results

QOL (SGRQ)

- Azithromycin: + 2.8
- Control: 0.6
- % > 4 units 43 vs 36
**MACRO Study (NEJM 2011)**

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial colonization</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Became macrolide-resistant</td>
<td>52%</td>
<td>57%</td>
</tr>
<tr>
<td>Became colonized</td>
<td>12%</td>
<td>31%</td>
</tr>
<tr>
<td>Macrolide-resistant</td>
<td>81%</td>
<td>41%</td>
</tr>
</tbody>
</table>
Why use azithromycin? // Summary

**Reasons to use**
- Decreases AECOPDs
- Improves QOL

**Reasons not to use**
- Hearing loss (?)
- Resistant organisms
- Herd immunity to macrolides
CLIP 2: “DECIDING BETWEEN MEDICINES”

Jean Rommes, PhD

In the role of a patient with COPD

Jerry Krishnan, MD, PhD

In the role of a Pulmonologist at UI Health
Learn more about RELIANCE
Visit RELIANCE-study.org

Become a Community Partner
(or nominate a colleague!)
Complete this brief form to nominate yourself or a colleague to learn more about being a RELIANCE Community Partner.

Robert Wise, MD
Please respond in the chat box.

Our next Roundtable is scheduled for July 26, what topics would you like to hear about?

Share your ideas in this 2-question survey.
Learn more about RELIANCE
Visit RELIANCE-study.org

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(or nominate a colleague!)
Complete this brief form to nominate yourself or a colleague to learn more about being a RELIANCE Community Partner.
THANK YOU!
APPENDIX
Roflumilast or azithromycin to reduce COPD exacerbations (RELIANCE)

Overview of trial design

- Up to 3,200 people with COPD associated with chronic bronchitis hospitalized for COPD exacerbation in past 12 months
- Evaluate guideline-recommended options for preventative care with established efficacy compared with placebo
- Chronic azithromycin vs. roflumilast as used in routine care, with randomization to select initial therapy
- COPD Foundation PPRN-led non-inferiority comparative effectiveness trial, stratified by site and current/past smoking status, followed 6-36 mos
- Primary outcome: All-cause hospitalization or death (self-report via call center, EHR, claims, NDI, Medicare data in subset)
Roflumilast or azithromycin to reduce COPD exacerbations (RELIANCE)

Overview of trial design: **secondary outcomes**

- All-cause individual events: hospitalization, emergency department visit, urgent care visit, and death (EHR, claims, self-report, NDI)
- Single-item PROMIS measures (physical function, sleep disturbance, fatigue, anxiety, depression; self-report)
- Adverse events (self-report, EHR)
- Medication adherence (self-report, Medicare data in subset); Crossover (self-report, Medicare data in subset, EHR); Treatment discontinuation (self-report, Medicare data in subset, EHR); Out-of-pocket costs (self-report), Weight (self-report)
**Inclusion criteria**

1. Patient and treating clinician considering treatment intensification with roflumilast or azithromycin to reduce the risk of COPD exacerbations
2. Age ≥ 40 years
3. Current or past smoker ≥ 10 pack-years
4. Diagnosis of severe COPD and associated chronic bronchitis
5. Hospitalized with a diagnosis of COPD exacerbation in the past 12 mos OR hospitalized with a diagnosis of respiratory complications associated with COVID-19 in the past 12 mos
6. Current medications include LAMA, LABA/LAMA, ICS/LABA
7. English speaking (Spanish coming soon)

**Exclusion criteria**

1. Unable or declines informed consent
2. History of intolerance to study medications
3. Current treatment of 30 or more days with roflumilast
4. Known hypersensitivity
5. Moderate to severe liver impairment
6. Current pregnancy
7. Declines to provide social security number or health insurance claims number
8. Any other clinician-determined exclusion as per their clinical practice.


**GOLD 2022 Report**

**Exacerbations**

- In patients who develop further exacerbations on LABA/LAMA therapy we suggest two alternative pathways. Blood eosinophil counts <100 cells/μL can be used to predict a low likelihood of a beneficial ICS response:
  - Escalate to LABA/LAMA/ICS. A beneficial response after the addition of ICS may be observed at blood eosinophil counts ≥ 100 cells/μL, with a greater magnitude of response more likely with higher eosinophil counts.
  - Add roflumilast or azithromycin (see below) if blood eosinophils < 100 cells/μL.

- In patients who develop further exacerbations on LABA/ICS therapy, we recommend escalation to triple therapy by adding a LAMA. Alternatively, treatment can be switched to LABA/LAMA if there has been a lack of response to ICS treatment, or if ICS side effects warrant discontinuation.

- If patients treated with LABA/LAMA/ICS who still have exacerbations the following options may be considered:
  - Add roflumilast. This may be considered in patients with an FEV1 <50% predicted and chronic bronchitis. particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.
  - Add a macrolide. The best available evidence exists for the use of azithromycin, especially in those who are not current smokers. Consideration to the development of resistant organisms should be factored into decision-making.
ACCP/CTS, 2015

PICO 3 Recommendations:

26. For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, we suggest the use of a long-term macrolide to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: This recommendation places high value on the prevention of COPD exacerbations. However, clinicians prescribing macrolides need to consider in their individual patients the potential for prolongation of the QT interval and hearing loss as well as bacterial resistance. The duration and exact dosage of macrolide therapy are unknown.

29. For patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation in the previous year, we suggest the use of roflumilast to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: Clinicians prescribing roflumilast need to advise their patients of the potential side effects of weight loss and diarrhea. Patients may have to discontinue the therapy because of side effects. The decision to prescribe this medication should also be informed by the fact that there are limited data for supplemental effectiveness in patients concurrently using inhaled therapies.

ERS/ATS recommendation
In patients who have COPD with severe or very severe airflow obstruction, symptoms of chronic bronchitis and exacerbations despite optimal inhaled therapy, we suggest treatment with roflumilast to prevent future exacerbations (conditional recommendation, moderate quality of evidence).

ERS/ATS recommendation
For patients who have COPD with moderate to very severe airflow obstruction and exacerbations despite optimal inhaled therapy, we suggest treatment with a macrolide antibiotic to prevent future exacerbations (conditional recommendation, low quality of evidence).