RELIANCE
RofLumilast or Azithromycin to preveNT COPD Exacerbations

QUARTERLY CLINICAL ROUNDTABLE SERIES

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

EXAMPLE DISCUSSION BETWEEN A PATIENT AND HER PHYSICIAN

Stephen Rennard, MD

Richard Albert, MD

WHY USE AZITHROMYCIN OR ROFLUMILAST

RELIANCE

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).


Jerry Krishnan, MD, PhD


Jean Rommes, PhD


Stephen Rennard, MD


Richard Albert, MD


Robert Wise, MD

Oscar win!

“DECIDING BETWEEN MEDICINES”

New Category:
Best Real World Drama

Jerry

Jean Rommes, PhD

Jerry Krishnan, MD, PhD

Jerry

Jean Rommes, PhD

In the role of a patient with COPD

CLIP 1: "DECIDING BETWEEN MEDICINES"

Jerry Krishnan, MD, PhD

In the role of a Pulmonologist at UI Health

Why use roflumilast?

Stephen Rennard, MD

Steve

The RELIANCE Study

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

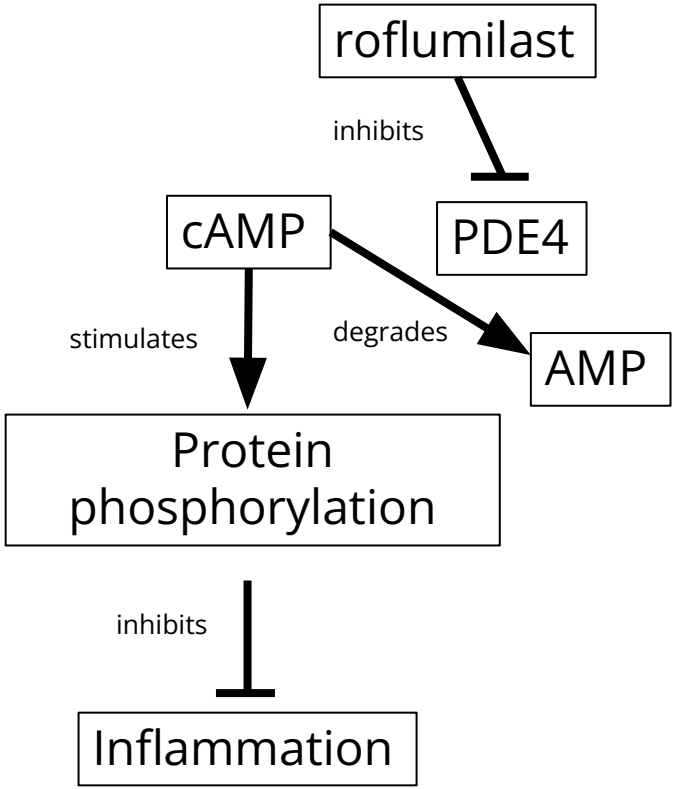
Equipoise with respect to the questions being addressed

In patient with chronic bronchitis…

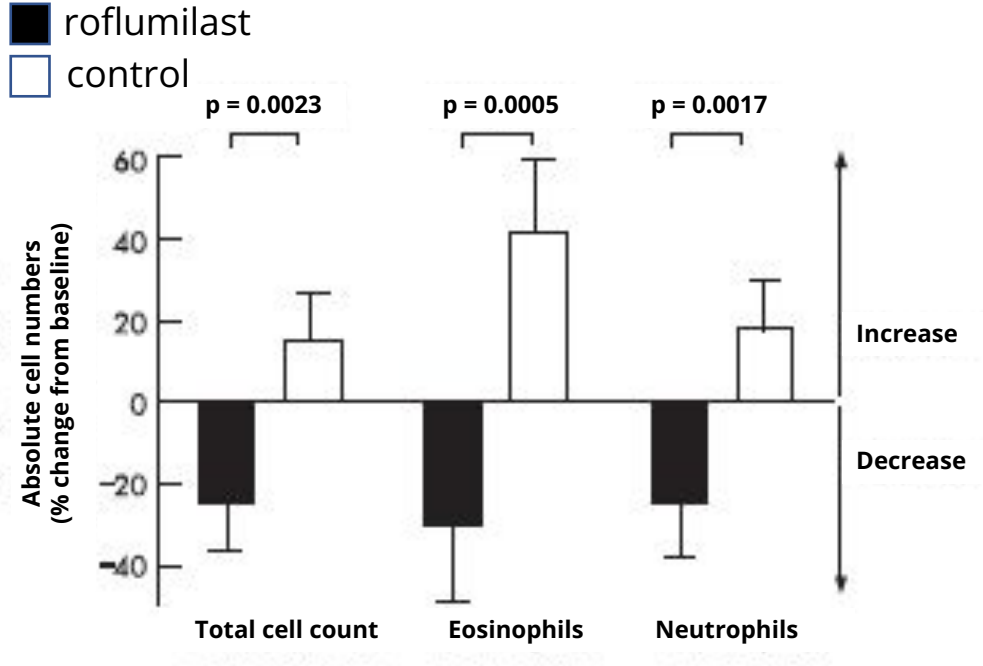
- Is roflumilast better, worse, or similar to azithromycin in reducing the risk of hospitalization or death?
- Which medication is better tolerated?

Roflumilast for COPD Exacerbations

1. **Rationale**
2. **Data on efficacy**
   Indicated population (chronic bronchitis)
3. **Adverse events**
   Dose up-titration
4. **Summary**



Change in sputum inflammatory cells



Grootendorst et al. Thorax 2007;62:1081–1087

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

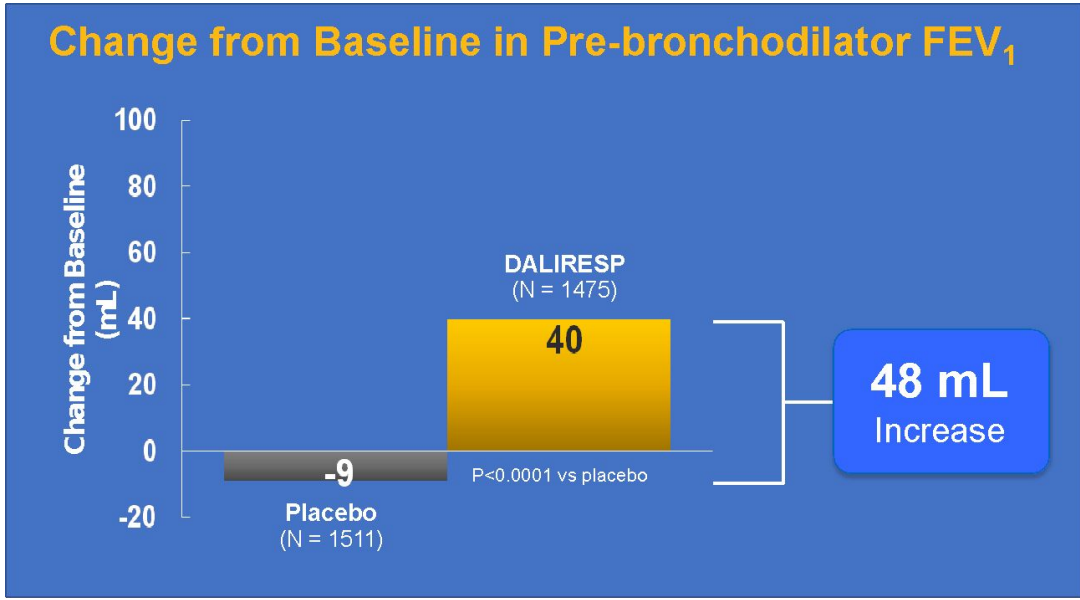
At least one hospitalized exacerbation or event requiring systemic steroids

Intervention

Roflumilast (500ug vs. placebo)

52 weeks

Roflumilast improves airflow:



Calverley et al. Lancet 374: 685, 2009

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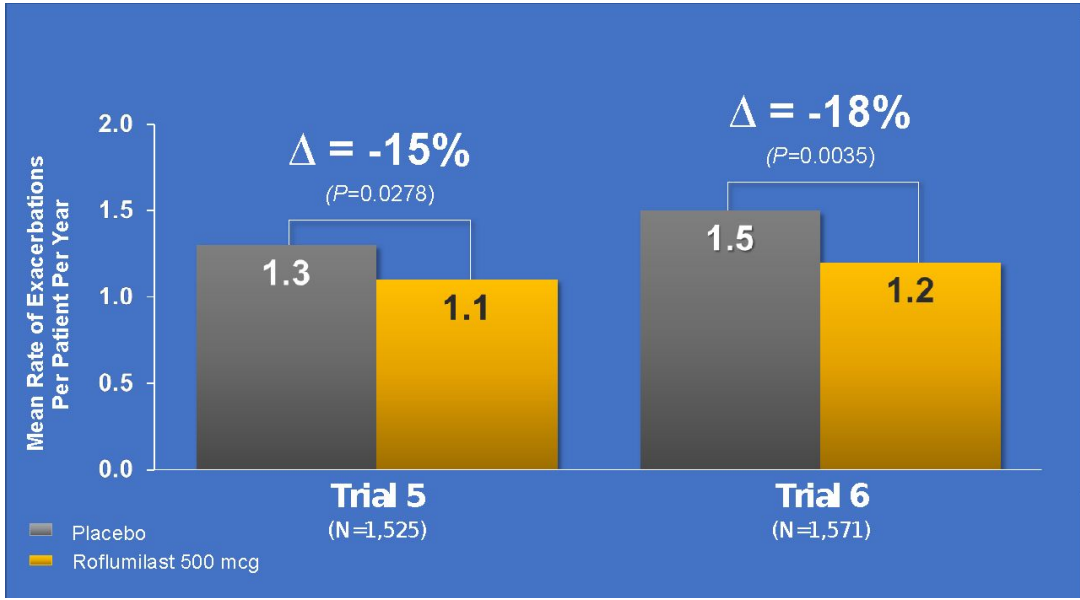
Roflumilast (500ug vs. placebo)

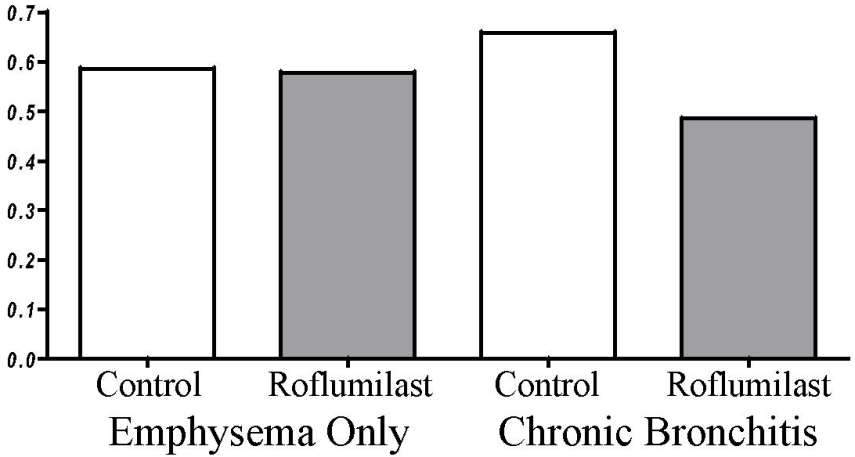
52 weeks

Roflumilast reduces exacerbations



Calverley et al. Lancet 374: 685, 2009

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

Rennard et al. Respir Res 12(1):18, 2011

Prior hospitalization: efficacy of roflumilast

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

Parameter	Number of Participants at Risk		Event Rate (95% CI)		Roflumilast vs. Placebo Rate Ratio (95% CI)	*P* Value
	Roflumilast 500 μg (*n* = 2,147)	Placebo (*n* = 2,140)	Roflumilast 500 μg	Placebo		
Age						
≤65 yr	1,167	1,176	1.01 (0.92–1.11)	1.14 (1.04–1.25)	0.89 (0.78–1.01)	0.0776
>65 yr	980	964	1.00 (0.90–1.12)	1.17 (1.05–1.29)	0.86 (0.74–0.99)	0.0419
Sex						
Male	1,539	1,519	0.89 (0.82–0.98)	1.09 (1.00–1.18)	0.82 (0.73–0.93)	0.0016
Female	608	621	1.34 (1.18–1.51)	1.33 (1.18–1.50)	1.01 (0.85–1.18)	0.9510
Race						
White	1,875	1,887	0.98 (0.91–1.06)	1.12 (1.04–1.21)	0.88 (0.79–0.97)	0.0148
Other	272	253	1.49 (1.14–1.93)	1.76 (1.35–2.30)	0.84 (0.64–1.11)	0.2247
Baseline weight						
<60 kg	486	491	1.36 (1.18–1.56)	1.45 (1.27–1.66)	0.94 (0.78–1.13)	0.4900
≥60 kg	1,661	1,649	0.92 (0.85–1.00)	1.07 (0.99–1.16)	0.86 (0.77–0.96)	0.0088
Smoking status						
Current	873	896	1.01 (0.90–1.13)	1.15 (1.03–1.28)	0.88 (0.75–1.03)	0.1033
Former	1,274	1,244	1.02 (0.93–1.12)	1.16 (1.06–1.27)	0.88 (0.77–1.00)	0.0439
Previous exacerbations						
2	1,729	1,735	0.92 (0.84–1.00)	1.00 (0.93–1.09)	0.91 (0.82–1.02)	0.1165
>2	394	388	1.63 (1.39–1.90)	2.06 (1.78–2.37)	0.79 (0.65–0.96)	0.0160
COPD severity						
Severe	1,355	1,397	0.87 (0.79–0.95)	0.97 (0.88–1.06)	0.90 (0.79–1.02)	0.0992
Very severe	765	719	1.28 (1.15–1.44)	1.55 (1.39–1.74)	0.83 (0.71–0.96)	0.0124
Concomitant LAMA use						
Yes	1,225	1,215	1.21 (1.11–1.33)	1.37 (1.26–1.49)	0.89 (0.78–1.00)	0.0563
No	922	925	0.83 (0.73–0.93)	0.96 (0.86–1.08)	0.86 (0.73–1.01)	0.0662
No. of hospitalizations in prior 12 mo						
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
Baseline total CAT score						
<10	219	197	0.61 (0.46–0.79)	0.82 (0.64–1.05)	0.74 (0.53–1.03)	0.0769
≥10	1,926	1,941	1.05 (0.98–1.14)	1.18 (1.10–1.27)	0.89 (0.80–0.99)	0.0262

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

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Greater than 2% on drug and drug > placebo

Adverse Reactions (Preferred Term)	Treatment	
	DALIRESP (N=4438) n (%)	Placebo (N=4192) n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Roflumilast package insert

Greater than 2% on drug and drug > placebo

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Roflumilast package insert

Suicide-related

	COPD safety pool		
	placebo (N=5,491) n (%)	rof500 (N=5,766) n (%)	rof250 (N=797) n (%)
Suicide attempt	–	2 (0.03)	–
Suicidal ideation	1 (0.02)	–	–
Completed suicide	–	1 (0.02)	–

Greater than 2% on drug and drug > placebo

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	DALIRESP (N=4438) n (%)	Placebo (N=4192) n (%)
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Roflumilast package insert

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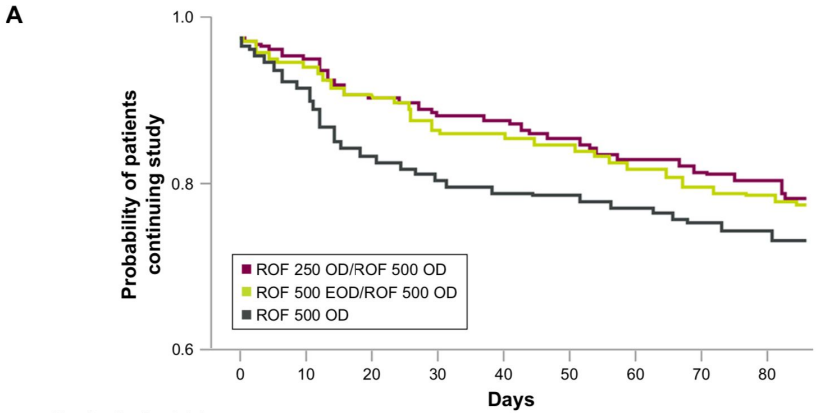
Suicide attempt	–	2 (0.03)	–
Suicidal ideation	1 (0.02)	–	–
Completed suicide	–	1 (0.02)	–

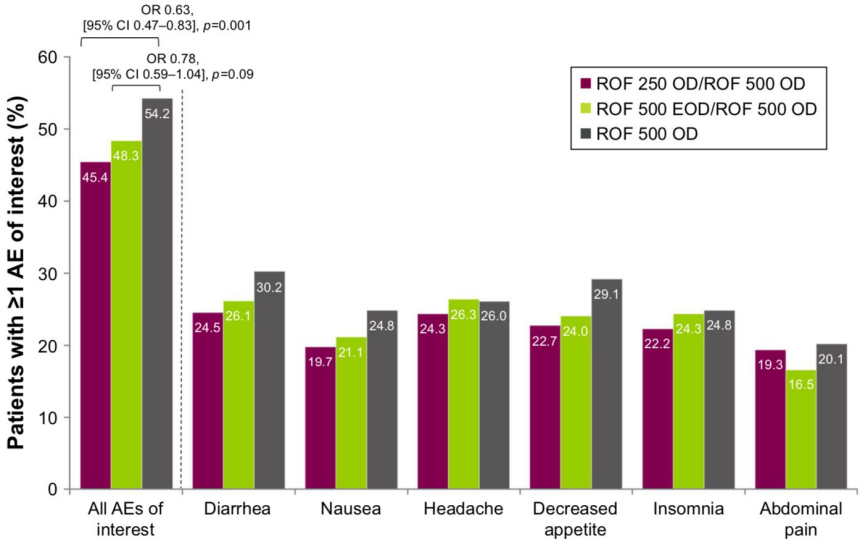
Contra-indications:
Moderate to severe liver impairment (Child-Pugh B or C)

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

Dose up-titration



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



Watz et al. Int. J COPD 13:813–822, 2018

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

Rick

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

Several treatments reduce AECOPDs

- ICS
- LABA
- LAMA

Despite all three: 1.4 AECOPD/yr

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)

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- RCT in 1142 patients
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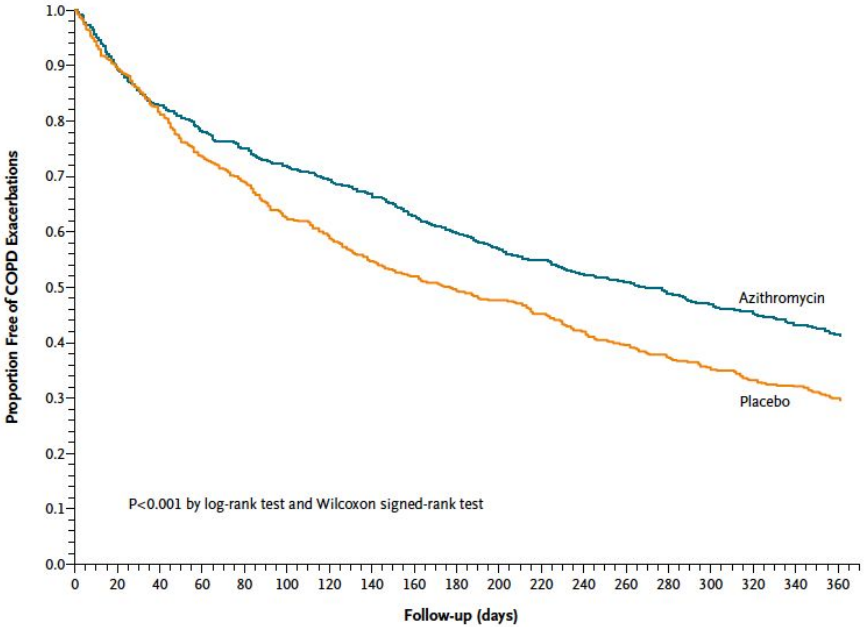

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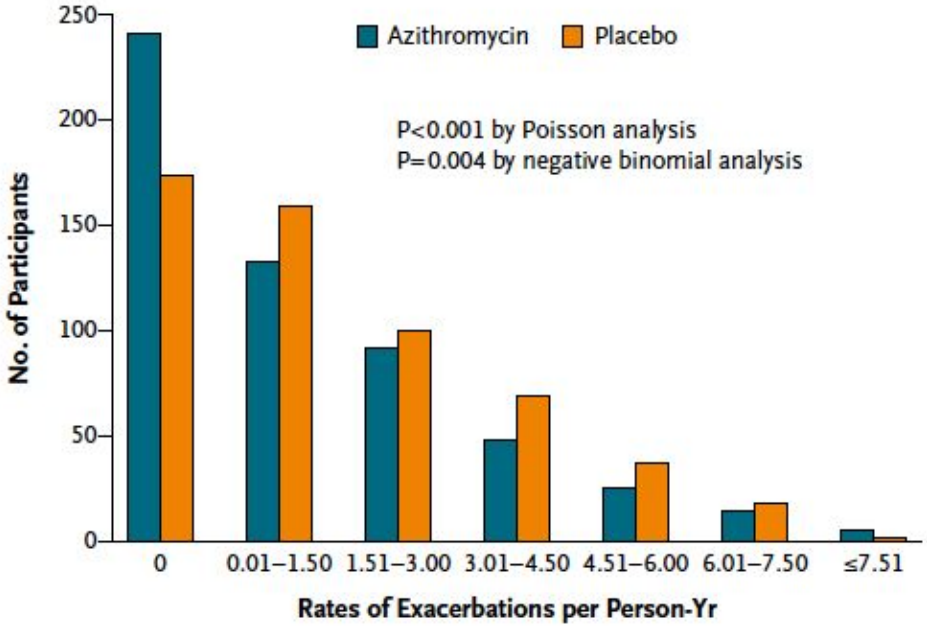

MACRO Study (NEJM 2011)

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

MACRO Study (NEJM 2011)

Results

QOL (SGRQ)

- Azithromycin: + 2.8
- Control: 0.6
- % > 4 units 43 vs 36

MACRO Study (NEJM 2011)

	Azithromycin	Control
Initial colonization	14%	15%
Became macrolide-resistant	52%	57%
Became colonized	12%	31%
Macrolide-resistant	81%	41%

Reasons to use

- Decreases AECOPDs
- Improves QOL

Reasons not to use

- Hearing loss (?)
- Resistant organisms
- Herd immunity to macrolides

Jean Rommes, PhD

In the role of a patient with COPD

CLIP 2: "DECIDING BETWEEN MEDICINES"

Jerry Krishnan, MD, PhD

In the role of a Pulmonologist at UI Health

Summary and Q&A

Robert Wise, MD

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.

Bob

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.

Summary and Q&A

Robert Wise, MD

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Bob

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)

RELIANCE trial eligibility criteria

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.

Roflumilast or azithromycin to reduce COPD exacerbations (RELIANCE)
For reference

GOLD 2022 Report

Exacerbations

- In patients who develop further exacerbations on LABA/LAMA therapy we suggest two alternative pathways. Blood eosinophil counts <100 cells/uL 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/uL, with a greater magnitude of response more likely with higher eosinophil counts.
    - Add **roflumilast** or **azithromycin** (see below) if blood eosinophils < 100 cells/uL.
- 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.

Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.org. Accessed 4/4/2022

RELIANCE

Roflumilast or azithromycin to reduce COPD exacerbations (RELIANCE)
For reference

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.

Criner, et al. 2015. Prevention of Acute Exacerbation of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. CHEST. DOI: 10.1378/chest.14-1677

Roflumilast or azithromycin to reduce COPD exacerbations (RELIANCE)
For reference

ERS/ATS, 2017

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).

Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2017; 50: 1602265