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Rebuttal From Dr Rho et al

We appreciate the thoughtful comments of Drs Suissa and Rabe.¹ In many respects, regarding the specifics of the roflumilast trials, there is little disagreement. We concur with the authors that roflumilast has “rather frequent side effects, which have led to significant premature discontinuations in clinical trials.” A Cochrane meta-analysis confirms that patients receiving roflumilast are more likely to experience diarrhea, nausea, and headache and more likely to discontinue medication because of adverse events than patients receiving placebo.² Nevertheless, there are some contrasts and clarifications worth noting.

First, we do not fault the roflumilast studies *because* they are industry sponsored. We fault them because of their heavily restricted inclusion and exclusion criteria and, in certain cases, reliance on end points of dubious clinical significance. That they are industry sponsored may provide some explanation for why large, costly clinical trials would be conducted that avoid pragmatic questions.

Second, one point of disagreement is the role of cessation of inhaled corticosteroids (ICSs). Drs Suissa and Rabe¹ argue that, “cessation of ICSs or other drugs at randomization should be expected to have a similar effect in both the roflumilast and placebo groups.” However, it is entirely possible that the roflumilast temporizes the harm of ICS discontinuation. This biologic

effect would be distinct from the question of whether the drug provides benefit beyond ICS.

Third, the Cochrane analysis demonstrates that roflumilast has little impact on quality of life or symptoms. No improvement in mortality was appreciated, though the authors confirm the drug decreases exacerbations.² Additionally, in that report, roflumilast was linked to an increase in psychiatric disturbances, which another analysis confirms.² Other groups have also found an increase in atrial fibrillation among roflumilast users.³

Finally, it appears future roflumilast trials may be better but remain far from good. The forthcoming Roflumilast in the Prevention of COPD Exacerbations While Taking Appropriate Combination Treatment (REACT) trial will randomize patients already on a long-acting β -agonist/ICS combination to roflumilast or placebo. Patients are allowed to use long-acting muscarinic antagonist medication, with short-acting β -agonist as rescue. However, the protocol is unclear as to whether short-acting antimuscarinics, such as ipratropium, will be permitted.

Notably, the inclusion criteria of the REACT study mandate that patients must have had at least two COPD exacerbations in the past 12 months. Over the same period, these patients must have remained on stable doses of long-acting β -agonist/ICS and long-acting muscarinic antagonist medication (despite those two exacerbations).⁴ Additionally, the REACT study uses a 4-week placebo run-in period. If during this time a patient has an exacerbation, he/she cannot be randomized until symptoms cease. If medication compliance is < 80%, the patient cannot be randomized. All of these choices in trial design undermine generalizability.

The results of the REACT study will be applicable only to patients who have had two more COPD exacerbations in the past year, but none in the past month, with no changes to the dose of key therapies as a result. The question will again arise if this trial is appropriate, or instead whether inclusion and exclusion criteria are so limiting that the trial fails to answer a meaningful question.

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