

Benefits and harms of roflumilast in moderate to severe chronic obstructive pulmonary disease

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Appendix

Gail et al. approach to benefit-harm assessment

Gail et al.¹ developed an approach to benefit-harm assessment that combines data on treatment effects, baseline risks, and relative importance of outcomes to provide a net benefit-harm index for decision-making. For a COPD patient at certain age, sex and with a certain baseline risk of exacerbations at treatment initiation, we can use this approach to calculate the net benefit-harm index that indicates whether roflumilast increases or decreases the occurrence of patient-centered outcomes overall (weighted by relative importance of outcomes) as compared to placebo over one year.

To perform this approach, we first calculate the number of cases expected ($N_{x,p}$) without roflumilast for each outcome per 10,000 patients over one year, considering death as a competing risk. We calculate the numbers using equation (1) with the data on incidence rates and mortality rates stratified by age and sex:

$$(1) N_{x,p} = 10,000 * [I_x / (I_x + M)] * \{1 - \exp[-1 * (I_x + M)]\}$$

where $N_{x,p}$ is the expected number of cases for a specific outcome x per 10,000 patients over one year without roflumilast. I_x is the incidence rate for outcome x (baseline risk) and M is the mortality rate.

We can then calculate the corresponding number of cases expected ($N_{x,t}$) per 10,000 patients with COPD if treated with roflumilast over one year following equation (2):

$$(2) N_{x,t} = 10,000 * [R_x * I_x / (R_x * I_x + M)] * \{1 - \exp[-1 * (R_x * I_x + M)]\}$$

where $N_{x,t}$ is the expected number of cases for a specific outcome x per 10,000 patients with COPD if treated with roflumilast over one year. I_x is the incidence rate for outcome x and M is the mortality rate. In contrast to equation (1), the relative risk of roflumilast on outcome x (R_x) is applied in equation (2).

We use equation (3) to calculate the differences (N_x) in the numbers of cases with and without roflumilast ($N_{x,p} - N_{x,t}$):

$$(3) N_x = N_{x,p} - N_{x,t}$$

Using equation (4), we calculate a net benefit-harm index as the sum of the difference in cases for each outcome weighted by their relative importance:

$$(4) \text{Index} = \sum(W_x * N_x)$$

where N_x is the difference for outcome x and W_x is the weight (relative importance) for outcome x .

The index is a synthesis of all data elements and represents a net benefit-harm comparison. A positive index indicates that roflumilast provides more benefit than harm, and a negative index indicates that roflumilast provides more harm than benefit. As described by Gail et al., we can use simulation to consider the statistical uncertainty (random variability) of the treatment effects for the outcomes.¹ We obtain 10,000 independent samples for each net benefit-harm index (per age, sex and baseline risk of exacerbations) to calculate the probability of roflumilast being beneficial as the proportion of estimates that are positive. In this study, we calculated the net benefit-harm indexes for different patient profiles and using different relative weights. The simulation was done using R statistical software version 3.0.1.

Reference

1. Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst* 1999;91(21):1829-46.