CORRESPONDENCE

The Pharmacological Treatment of Chronic Obstructive Pulmonary Disease

by Prof. Dr. med. Adrian Gillissen, Prof. Dr. med. Peter Haidl, Prof. Dr. med. Martin Kohlhäufel, Prof. Dr. med. Dr. rer. nat. Klaus Kroegel, Dr. med. Thomas Voshaar, and PD Dr. med. Christian Gessner in issue 18/2016

Missing Information

From the primary care viewpoint this article leaves almost nothing to be desired, were it not for one slight blemish (1). Although the authors—in line with the tenets of evidence-based medicine—state the number needed to treat (NNT), and thus the absolute risk reduction, in their presentation of the studies on inhaled corticosteroids and β_2 -mimetics, precisely this information is missing from their interpretation of the REACT study on the phosphodiesterase-4 inhibitor roflumilast. (And, by the way, one value is reproduced incorrectly: it should be “0.959 in placebo”.) Even if one overlooks the methodological weaknesses of the REACT study, the question remains of whether a positive recommendation can be issued for a pharmacological treatment based on a NNT of 735 patients for a year to avoid one exacerbation. It should be noted that the most frequently reported serious adverse events were exacerbations and pneumonia (2).

This question should also, by the way, be addressed to the representatives of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which is mentioned in the article.

The authors are particularly generous in assigning a guideline recommendation of evidence recommendation grade B to two studies with flawed methods and serious conflicts of interest (3, 4) in which, among other things, a NNT of 434 was ascertained based on 52 weeks. This is unfortunately anything but transparent evidence-based medicine and mars the otherwise good impression of this review.

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Conflict of interest statement

The author declares that no conflict of interest exists.

In Reply:

The REACT study, which evaluated the efficacy of roflumilast given together with LABA and LAMA and had as its primary endpoint reduction of moderate and severe exacerbations of chronic obstructive pulmonary disease (COPD) per patient and year, yielded the following results (1):

In the intention to treat population the reduction in the COPD exacerbation rate versus placebo was 13.2% with Poisson regression analysis, corresponding to a risk rate reduction of 0.868 [95% CI 0.753; 1.002], $p = 0.0529$, and 14.2% with binomial regression analysis, corresponding to a risk rate reduction of 0.858 ([0.740; 0.995], $p = 0.0424$). The analyses of the per-protocol population were even more favorable. Moreover, the rate of severe COPD exacerbations (secondary endpoint parameter) went down by more than 20% and lung function parameters improved. On the other hand, roflumilast did not change the CAT score. Adverse effects were reported in 67% of the roflumilast group and 59% of the placebo group. The most frequently occurring adverse effects were COPD exacerbations, diarrhea, and weight loss. The conflicts of interest were stated in the respective studies.

The number needed to treat (NNT) has been supplied in various publications on roflumilast (2, 3). In the study by Bateman et al., for example, the NNT to avoid one exacerbation per patient and year was 3.2 (3). The NNT in the REACT study is most likely higher because roflumilast was used in a cohort of COPD patients in whom other treatments had failed. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the use of roflumilast as an additional measure to lower the elevated exacerbation rate in patients with chronic bronchitis and severe or extremely severe COPD whose disease was not sufficiently controlled by their previous medication (evidence recommendation grade B). Our review focused principally on the ICS evaluation of treatment for COPD, hence the reference to the GOLD recommendation with regard to roflumilast (1, 4).

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Conflict of interest statement

Prof. Gillissen has acted as a paid consultant for Chiesi, Teva, Elpen, and Berlin-Chemie. He has received reimbursement of congress attendance fees from Chiesi and Teva, and has had travel costs paid by Chiesi, Teva, Boehringer Ingelheim, Elpen, Almirall, and Berlin-Chemie. He has been paid for giving lectures by AstraZeneca, Elpen, Chiesi, Boehringer Ingelheim, and Berlin-Chemie.