Roflumilast in COPD

To the Editor:

We read with interest the Point and Counterpoint editorials in *CHEST* (May 2014) by Suissa and Rabe[1] and Rho et al[2] about the appropriateness of industry-sponsored roflumilast trials. In the editorials, reference was made to the level of patient withdrawal as well as to the level of side effects experienced by patients receiving this drug during clinical trials.[2] In our real-world clinical experience, we have found both the reported side effect and drug discontinuation rates to be at far higher than reported levels.

Following the initial introduction of roflumilast to the Irish market, we carried out a retrospective review of all patients who received the drug as part of therapy at our institution to document efficacy with particular reference to the adverse events experienced, the discontinuation rate, and the perceived clinical benefit to treatment. Twenty-five patients with moderate to severe COPD were prescribed roflumilast, with 84% discontinuing treatment after a mean of just 3½ months. The most cited reason for stopping treatment was intolerance to side effects (81%), followed by a lack of clinical benefit (19%). Side effects were experienced by 72% of all patients, with nausea (52%), diarrhea (16%), and vomiting (12%) the most common. Our numbers, albeit small, are in stark contrast to the side effect profile reported in larger roflumilast studies in which discontinuation rates of 14% to 20% were reported as opposed to 84% of patients discontinuing treatment in our patient group.[3,4]

Our findings suggest that roflumilast has a high side effect burden leading to discontinuation of therapy among a majority of patients. Although we recognize that there may be a role for roflumilast in the treatment of COPD (20% of the patients did find an improvement in symptoms and in their quality of life), the decision to treat has to be tempered carefully against the side effect profile associated with it, at least in our real-world findings.

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Response

To the Editor:

We thank Dr Worndl and colleagues for their letter in response to our article,[1] which argued that industry-sponsored trials for roflumilast had been inadequately designed to best answer patient-centered questions as part of a Point and Counterpoint editorial debate.[1,2] Dr Worndl and colleagues raise an important point: The real-world side effects of roflumilast far exceed those seen in pivotal randomized trials. In their own analysis, they note that 84% of patients with moderate to severe COPD discontinued the drug. This number far exceeds the percentages quoted in randomized trials.

Other independent groups have noted similar inflated real-world rates of roflumilast discontinuation. A retrospective analysis of two hospitals in Barcelona, Spain, found that among 55 consecutive patients prescribed roflumilast according to local guidelines, 11 patients (20%) discontinued the drug within 12 weeks of starting it, and another 16 patients (29%) discontinued between 12 and 52 weeks.[3] Altogether, just less than one-half of

participants took the drug for < 1 year. Sixty-nine percent of participants experienced side effects in this study, with nausea, diarrhea, and weight loss commonly reported. Weight loss was greater in those who withdrew from treatment than in those who remained on therapy.

In a recent randomized study of roflumilast, the sponsor stopped providing participants with the drug at the end of 52 weeks, although the drug remained available commercially. Interestingly, only 6% and 7% of patients assigned to roflumilast or placebo, respectively, opted to take the medication in the poststudy period.[4]

Finally, others have noted that there are several discrepancies between the reporting of events in publications of pivotal trials and those that appear in the US Food and Drug Administration's independent tallying of the same safety data.[5] For instance, trial publications do not make it clear that 12 cases of diarrhea among users of roflumilast were so intractable that they required hospitalization.[6] Moreover, rates of psychiatric disturbances, such as increased suicidality, were noted solely by the Food and Drug Administration. In a more recent randomized trial of roflumilast, a history of depression with suicidal ideation or behavior is listed as exclusion criteria.[4]

Although larger studies are needed to provide better estimates of the real-world tolerability of roflumilast, thus far, the preliminary evidence appears unfavorable and is a marked departure from the randomized trials submitted for the drug's approval. Ironically, it may be these smaller, nonindustry-sponsored studies that shed further light onto the true impact of the severity of the side effects of roflumilast.

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