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Reply to Palmer *et al.*

From the Authors:

We thank Palmer and colleagues for their interest in our article (1). The authors have pointed out that, in our study, we have used, as maintenance therapy, subtherapeutic doses of budesonide/formoterol (200/6 μg, twice daily), as compared with other studies using twice this dose. Palmer and colleagues also raised concerns about whether patients would have greater benefits when using higher doses of budesonide/formoterol.

There are many clinical studies investigating the effect of the combination of budesonide/formoterol in patients with asthma but only a few in patients with chronic obstructive pulmonary disease (COPD). Notably, in most of the clinical studies with COPD patients, two dosage schemes for budesonide/formoterol were tested (320/9 μg [twice daily] and 160/9 μg [twice daily] [2–4]), the latter dosage corresponding to the dosage that we have used as low-maintenance therapy in our study. The efficacy of both dosages was comparable, as assessed by the improvement in lung function, the reduction in the exacerbation rate, and the improvement in quality of life.

Rennard and colleagues (2), in a 1-year, randomized, double-blind, placebo-controlled, parallel group, multicenter study of 1,964 patients, have shown that in the budesonide/formoterol (160/9 μg, twice daily) group, the percentage of patients who discontinued the study was similar for those who were previously receiving an inhaled corticosteroid (ICS) (29.5%) and those who were not (28.2%). In the same study, improvements in 1-hour predose and postdose FEV_1 were significantly greater for both budesonide/formoterol dosages, compared with placebo, and overall maintained over the 12-month treatment period for both budesonide/formoterol dosages. Mean FEV_1 at 12 hours and baseline-adjusted average 12-hour FEV_1 were significantly improved with both budesonide/formoterol dosages compared with placebo on the day of randomization and at the end of treatment. Time to first COPD exacerbation was significantly prolonged with both budesonide/formoterol dosages compared with placebo. In addition, significant reductions in the overall number of exacerbations per patient-treatment year were observed with both dosages. Furthermore, improvements in St. George's Respiratory Questionnaire total score were significantly greater for both budesonide/formoterol dosages compared with placebo and for budesonide/formoterol (160/9 μg) compared with formoterol alone, thus suggesting a similar efficacy of the low-dose budesonide/formoterol regarding lung function improvement, exacerbation rate, and time to exacerbation and a superior effect regarding quality of life.

As expected, local side effects of ICS (aphonia, dysphonia, oral candidiasis, and candidiasis) were more frequent with the higher dose of budesonide/formoterol (320/9 μg) compared with the lower dose (160/9 μg) (10.3% vs. 5.7%). Cardiac-related adverse events such as hypertension were also higher for the budesonide/formoterol (360/9 μg) group compared with the budesonide/formoterol (160/9 μg) group (2.4% vs. 1.6%).

In the study by Tashkin and colleagues (3), a 6-month, randomized, double-blind, placebo-controlled, parallel group, multicenter study of 1,704 patients, dyspnea measured using the breathlessness diary and health-related quality-of-life scores were significantly improved with both dosages of budesonide/formoterol (360/9 and 160/9 μg, twice daily) compared with budesonide, formoterol, and placebo. Furthermore, the number of exacerbations per patient-treatment year requiring treatment with oral corticosteroids and/or hospitalization was 20–25% lower with the budesonide/formoterol treatments compared with formoterol and placebo. The incidence of nonfatal serious adverse events was higher in the 320/9-μg group (6.1%) than in the 160/9-μg group (4.3–4.6%).

Sharafkhaneh and colleagues (4), in a double-blind, randomized study with 1,219 patients, have shown that budesonide/formoterol (160/9 μg, twice daily) reduced exacerbation rates by 25.9%. Exacerbation rates including antibiotic treatment were reduced by 18.7%. Even though both budesonide/formoterol doses were well tolerated, pneumonia adverse events occurred in 4.7% with the dose of 160/9 μg versus 6.4% with the dose of 320/9 μg.

Taken together, all three randomized controlled trials (RCTs) show a similar efficacy for both doses regarding exacerbation rate, lung function, and quality of life but a lower incidence of side effects. Thus, in our view, the published evidence justifies the use of the lower dose of budesonide/formoterol as maintenance therapy for patients with COPD.

In line with the above evidence from the limited RCTs that have investigated the efficacy of budesonide/formoterol (5), numerous RCTs investigated the effect of fluticasone/salmeterol in doses corresponding to 250/50 μg, twice daily, in studies performed in the United States (6) and 500/50 μg, twice daily, in studies performed in Europe (7). Despite the fact that the dose used in the United States is one-half the dose used in Europe, the efficacy of both dose regimens was comparable. Improvement in FEV_1 was 33% for the dose of 250/50 μg and 40% for the dose of 500/50 μg. Similarly, the annual rate of exacerbations was decreased by 30.5% and 35%, respectively, for the dose of 250/50 μg and 500/50 μg (6, 7). These data provide further evidence that the low-maintenance dose we have used in our study was both effective and safe for the patients.

Palmer and colleagues also raised concerns about the dose of long-acting β-agonist (LABA)/ICS that the patients were receiving before the trial. Of 450 patients who were enrolled,

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only 84 patients (25.7%) were receiving LABA/ICS at a higher dose than the maintenance dose we used in this trial. Of those 84 patients, only 13 patients (15.5%) had an upper respiratory tract infection (URTI) within 3 months of inclusion, and of those only four patients had an exacerbation within 21 days of URTI. Even though conflicting findings exist on the risk of withdrawal of ICS in COPD, a meta-analysis has shown that ICS withdrawal did not significantly increase the overall rate of COPD exacerbations (8). Furthermore, despite the fact that ICS withdrawal significantly impaired both lung function and quality of life, this was not clinically significant (8). Based on the weak evidence for a link between ICS withdrawal and exacerbation increase and because our study did not involve withdrawal of ICS, but rather a decrease in the dosage in a minority (25.7%) of the enrolled patients, we do not believe that the change in ICS dose would be related to an increase in exacerbation rate. Most importantly, the primary objective of our study was not to investigate the efficacy of the combination therapy with budesonide/formoterol to decrease exacerbations, as this has been extensively evaluated in previous studies (2–4). The primary objective of our study was to investigate whether intensified combination therapy with ICS/LABA, at the onset of URTI, could reduce exacerbations within 21 days of the URTI onset in patients with COPD receiving a low-maintenance dose of ICS/LABA. To this end, there is no evidence in the literature that dosage reduction of ICS is associated with increased URTI.

Palmer and colleagues have also pointed out that there was quite a high death rate (11%) in our study, compared with previous COPD trials such as the FLAME (Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations) trial (1.4%). The death rate reported in our study was similar to the rate of 12% previously reported in the PROMISE (Predicting Outcome Using Systemic Markers in Severe Exacerbations of COPD) study (9), a European, multicentric, observational study, involving eight countries and 11 institutions, with similar inclusion criteria and the same mean follow-up of 24 months as our study. The lower death rate (1.4%) reported in the FLAME study may be attributed to the shorter follow-up time (12 mo), as compared with our study, as well as to the numerous exclusion criteria (33 main exclusion criteria and many more subcriteria) applied (10). In addition, it is important to highlight that all patients developing an exacerbation while taking a long-acting muscarinic antagonist alone during the run-in period in the FLAME study were excluded, resulting in a 37% dropout during the enrollment period (10).

In our investigator-initiated and -driven RCT, despite a rather low number of events, we were able to show that intensified therapy with ICS/LABA for 10 days at URTI onset significantly decreased the risk of severe exacerbations and the risk of any exacerbation in patients with more severe disease. However, a larger study would be needed to detect a potential effect of this therapeutic approach on mortality. ■

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Combination Nintedanib and Pirfenidone for Treatment of Idiopathic Pulmonary Fibrosis

To the Editor:

We had the pleasure of discussing Vancheri and colleagues' recent trial ("Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis: Results of the INJOURNEY Trial" [1]) at our Twitter-based journal club (@Resp&Sleep JC, #rsjc) on February 22, 2018.

INJOURNEY concluded that combination therapy for 12 weeks had a manageable safety and tolerability profile in patients with idiopathic pulmonary fibrosis, but some important caveats were raised during our journal club discussion. Patients with previous intolerance to nintedanib were excluded, as were patients requiring treatment interruption or dose reduction in the run-in period. In the combination group, 19 of 53 patients discontinued pirfenidone prematurely, and seven of 53 patients discontinued nintedanib prematurely. Ultimately, only 34 of 53 patients in the dual-therapy group completed 12 weeks of treatment.

Our journal club participants questioned the authors' conclusion of tolerability given that less than two-thirds of study patients were able to complete the 12 weeks of therapy. This represents a high dropout rate, in an already highly selected group of patients. Hence, we are concerned about sampling bias and the external validity of the result. The short duration of the trial also raised concerns about long-term tolerability, as long-term treatment is usually required with antifibrotic medications (2).

Although the exploratory efficacy outcome is promising, larger trials are needed before we have enough data to help patients decide if the benefits of combination therapy outweigh the significant cost and potential effects on quality on life. Even so, with such a high dropout rate here, we wonder about the feasibility of a larger study. ■

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2. @nsitz. Patients in the combination therapy group had higher rates of diarrhea, nausea and vomiting than nintedanib alone. The trial only lasted for 12 weeks. I am concerned about long term tolerability. [posted 2018 Feb 22]. Available from: https://twitter.com/nsitz/status/966852490108067840.

Reply to Rajchgot *et al.*

From the Authors:

The INJOURNEY trial was designed to assess the safety, tolerability, and pharmacokinetics of nintedanib with add-on pirfenidone, compared with nintedanib alone, over 12 weeks of treatment in patients with idiopathic pulmonary fibrosis (IPF) (1). Rajchgot and colleagues express a concern regarding the exclusion of patients with previous intolerance to nintedanib, or who had a treatment interruption or dose reduction during the run-in period, from this trial. We believe that this approach will reflect future clinical practice if combination treatment is confirmed to have a positive benefit–risk profile in patients with IPF. Given the overlapping side effect profiles of the two available therapies, it seems very unlikely that a second antifibrotic therapy would be given to patients who are unable to tolerate one of these drugs. Similarly, a single-arm open-label study assessing the safety and tolerability of combination therapy with pirfenidone and nintedanib over 24 weeks enrolled patients who had been receiving pirfenidone for at least 16 weeks and had received a stable dose for 28 days without any moderate or severe adverse reactions (2). We politely refute the assertion that the INJOURNEY trial involved a highly selected group of patients: Both patients who were nintedanib naive prior to the run-in period and patients who were already taking nintedanib were eligible to participate. However, we acknowledge that patients were selected to participate in this trial on the basis of reasonable tolerability of nintedanib, as would be expected in clinical practice.

Rajchgot and colleagues correctly state that 64% of patients in the combination therapy arm and 82% of patients treated with nintedanib alone completed 12 weeks of treatment. It is important to note that not all patients discontinued treatment owing to adverse events. Because most side effects of nintedanib and pirfenidone occur within the first 3 months of treatment, the duration of treatment in the INJOURNEY trial was regarded as sufficient to explore the feasibility of combining these treatments. Furthermore, longer trials of nintedanib and pirfenidone administered individually have revealed no new safety signals compared with shorter trials (3, 4).

As we stated in our article (1), we agree with Rajchgot and colleagues that larger trials are needed to determine the risk–benefit profile of combination therapy with nintedanib and pirfenidone in patients with IPF. We believe that such trials would be feasible but

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