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Research letter

Concomitant Medications and Clinical Outcomes in Idiopathic Pulmonary Fibrosis

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Title: Concomitant Medications and Clinical Outcomes in Idiopathic Pulmonary Fibrosis

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To the editor:

Patients with idiopathic pulmonary fibrosis (IPF) frequently have a substantial burden of comorbidities [1]. Antifibrotic therapy is recommended to slow the progression of IPF [2]. Patients receiving antifibrotic therapy frequently receive concomitant medications for the management of comorbidities [1, 3-9]. Previous post hoc analyses of antacids, statins, metformin, anti-coagulants and angiotensin modulators in patients with IPF enrolled in Phase III randomised controlled trials (RCTs) have generated hypotheses on the impact of these treatments on IPF outcomes [3-9]. The effects of multiple concomitant medications in patients with IPF have been largely unexplored. The objective of the present analyses was to explore the association between use of combinations of frequently prescribed concomitant medications and disease outcomes in patients with IPF.

Patients who received placebo in ASCEND (Study 016; NCT01366209) and CAPACITY (Studies 004 and 006; NCT00287716 and NCT00287729) and patients randomised to receive placebo or interferon γ-1b in INSPIRE (NCT00075998; no treatment effect was observed) were included in the present analyses [10-12]. Eligibility criteria and data collection were previously described [10-12]. Baseline medication use was characterised by the drug/drug class and number of drug/drug classes patients were receiving. Drug/drug classes of interest were selected based on the number of patients and effects seen in previous analyses and pre-analyses [3-7]. The outcome was a composite endpoint of disease progression, defined as the first occurrence of absolute decline in percent predicted forced vital capacity (% predicted FVC) ≥10%, decline in 6-minute walk distance (6MWD) ≥50 m or death from any cause over 52 weeks. This composite endpoint was evaluated in ASCEND and in previous post hoc analyses of medication use in pooled data from ASCEND and CAPACITY [3-7, 10]. Associations between baseline medication use and the study outcome were estimated using Cox proportional hazard models; hazard ratios (HRs) were adjusted for age, sex, smoking status, baseline physiological function (% predicted FVC and % predicted diffusing capacity for

carbon monoxide), 6MWD, University of California, San Diego Shortness of Breath Questionnaire and comorbidities, which were selected for inclusion via the stepwise method. In the models, medication use was characterised using 2 independent binary variables and the pairwise combination of the 2 binary variables. Patients with missing baseline information were excluded from multivariable analyses.

The full analysis population comprised 1450 patients with IPF. At baseline, the most frequently reported concomitant medications were proton pump inhibitors (PPIs) (604 patients, [41.7%]), anti-thrombotics (including anti-aggregants) (604 [41.7%]), statins (568, [39.2%]), obstructive airway medications (497 [34.2%]) and anti-inflammatory medications (423, [29.2%]). Few patients were receiving these medications alone (without ≥1 concomitant medications) (PPIs, 54 patients [3.7%]; anti-thrombotics, 10 [0.7%]; statins, 13 [0.9%]; obstructive airway medications, 60 [4.1%]; anti-inflammatory medications, 33 [2.3%]). At baseline, 153 patients (10.6%) were receiving no medications, while 754 (52.0%) were receiving 1–3 medications and 543 (37.4%) were receiving ≥4 medications. The most frequent pairwise combinations of medications (with or without additional concomitant medications) were anti-thrombotics and statins (367; 25.3%), PPIs and anti-thrombotics (298; 20.6%) and PPIs and statins (273; 18.8%). At baseline, 77 unique combinations of medications were reported in 2 patients each (10.6%), and 342 unique combinations were reported in 1 patient each (23.6%).

At baseline, the most frequently reported comorbidities were hypertension (757 patients, [52.2%]), obesity (616 [42.5%]), hypercholesterolaemia (556 [38.3%]), cardiovascular disease (CVD) (386 [26.6%]), gastro-oesophageal reflux disease (GERD) (325 [22.4%]) and diabetes (304 [21.0%]). However, few patients reported these comorbidities alone (without ≥1 additional comorbidity; hypertension, 79 patients [5.5%]; obesity, 92 [6.3%]; hypercholesterolaemia, 48 [3.3%]; CVD, 15 [1.0%]; GERD, 32 [2.2%]; diabetes, 17 [1.2%]). Only 202 (13.9%) patients reported no comorbidities, while 23 unique combinations of comorbidities were reported in 2 patients each (3.2%), and 118 unique combinations were reported in 1 patient each (8.1%).

The HR (95% CI) for disease progression in bivariate analyses was 0.79 (0.62, 1.01; *P*=0.059) for angiotensin-converting enzyme inhibitor treatment, 0.91 (0.76, 1.08; *P*=0.272) for statins, 1.00 (0.84, 1.18; *P*=0.958) for PPI, 1.13 (0.94, 1.34; *P*=0.192) for obstructive airway medications, 1.14 (0.78, 1.65; *P*=0.505) for metformin, 1.07 (0.87, 1.31; *P*=0.527) for diabetes medications, 1.09 (0.87, 1.36; *P*=0.458) for angiotensin II receptor blockers (ARBs) and 1.14 (0.76, 1.72; *P*=0.534) for anti-coagulants.

Multivariable analyses explored potential interactions between pairwise combinations of concomitant medications and their association with disease progression in the overall population (**Figure**). Of 78 pairwise combinations of drugs/drug classes analysed, 5 suggested potentially decreased or increased risk of disease progression based on HRs for the interaction terms in the models: metformin and obstructive airway medications (HR, 0.30 [95% CI, 0.14, 0.63]), anti-inflammatory and obstructive airway medications (1.63 [1.09, 2.42]), ARBs and diabetes medications (1.71 [1.04, 2.80]), diabetes and thyroid medications (1.84 [1.01, 3.35]) and PPI and metformin (2.25 [1.06, 4.80]). None of the most frequently reported pairwise combinations, including statins and anti-thrombotics (25.3% of patients), PPIs and anti-thrombotics (20.6%), statins and PPIs (18.8%), PPIs and obstructive airway medications (16.4%), obstructive airway medications and anti-thrombotics (15.4%) and beta blockers and anti-thrombotics (15.4%), were associated with differences in IPF outcomes.

Disease progression was observed in 62 patients (40.5%) receiving 0 medications, 266 (35.3%) receiving 1–3 medications and 205 (37.8%) receiving ≥4 medications. The adjusted HR (95% CI) for disease progression was 0.908 (0.680, 1.213; *P*=0.51) in patients receiving 1–3 vs. 0 medications and 1.063 (0.779, 1.450; *P*=0.70) in patients receiving ≥4 vs. 0 medications. Meaningful differences in the primary outcome were not observed when patients were analysed with more-granular categories for number of medications (0, 1–2, 3–4, 5–6, 7–8 and 9–10).

In the absence of data from large registries of patients with IPF, these post hoc analyses of data from Phase III RCTs in patients with IPF highlighted heterogeneity in concomitant

medication use and comorbidities that are prevalent in the IPF population. However, these analyses found no association between the number of concomitant medications used and IPF progression. In these data, interactions between pairwise combinations of medications were associated with a broad range of HRs (HR range, 0.22–2.25), suggesting potential impacts on disease progression in patients with IPF, but the interpretation is limited.

GERD, CVD, hypertension and diabetes are frequently reported comorbidities that may impact the burden of disease in the IPF population [1, 13-15]. Use of medications that treat these comorbidities was not clearly associated with an increased risk of disease progression in this analysis, whether the medications were evaluated alone or in pairwise combinations. The exceptions to this observation were pairwise combinations of PPI and metformin, diabetes and thyroid medications, ARBs and diabetes medications and obstructive airway and anti-inflammatory medications (HR range, 1.63–2.25). The findings were mostly consistent with previous analyses that found no association between treatment with antacids, statins, metformin, anti-coagulants or angiotensin modulators and disease progression, although elevated mortality risk was observed in patients treated with anti-coagulants or ARBs, and decreased mortality risk was observed in patients treated with statins [3-7].

Importantly, we stress that the interpretation of these findings is limited by the post hoc nature of the analyses. Moreover, medication use was evaluated only at baseline, and thus some patients may have been misclassified at the time of disease progression. Drug dose and duration of use were not evaluated. Some analyses may have been underpowered to detect differences, as many combinations of medications were reported in small numbers of patients. The number of comparisons and hypotheses tested increased the likelihood of false positives. Furthermore, these findings may not be applicable to real-world populations of patients with IPF, who often have a greater burden of comorbidities and poorer overall health.

Currently, there is a lack of evidence on the safety and impact of combinations of common medications in the IPF population. Furthermore, whether combinations of common

medications affect IPF progression in patients receiving antifibrotic therapy remains an open question. These questions should continue to be examined in prospective registry studies and RCTs.

CONFLICT OF INTEREST

M.K. or his institution has received research grants and compensation for consulting and speakers bureau participation from Boehringer Ingelheim, Galapagos and Roche.

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D.W. and M.A. are employees of Policy Analysis Inc. (PAI).

K.U.K. is an employee of F. Hoffmann-La Roche Ltd.

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individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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FIGURE CAPTION

Figure. Multivariable models of concomitant medication use and disease progression*: results for interactions between pairwise combinations of concomitant medications. 6MWD, 6-minute walk distance; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; CCB, calcium channel blocker; FVC, forced vital capacity; HR, hazard ratio; PPI, proton pump inhibitor. * Disease progression was defined as the first occurrence of absolute decline in % predicted FVC ≥10%, decline in 6MWD ≥50 m or death from any cause over 52 weeks. † Adjusted for baseline demographics and clinical characteristics. HRs correspond to interaction terms (i.e., patients receiving both medication 1 and medication 2 vs. patients receiving only medication 1, only medication 2 or neither). Patients missing baseline information (n=55) were excluded from multivariable analyses.