Pirfenidone for Idiopathic Pulmonary Fibrosis, Thrombocytosis in Chronic Obstructive Pulmonary Disease Exacerbations, and a Longitudinal Study on E-Cigarettes

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Idiopathic pulmonary fibrosis (IPF) is life-limiting irreversible progressive lung scarring without a clear cause. Pirfenidone, an oral medication with anti-fibrotic mechanisms that are in part mediated by inhibition of expression of transforming growth factor-β1, is studied favorably in this trial (1).

In this well-designed 52-week multinational, randomized, placebo-controlled study, 555 patients were enrolled; 278 were assigned to receive pirfenidone, and 277 patients received placebo. Inclusion criteria were chosen carefully: patients were between 40 and 80 years of age, had a centrally confirmed diagnosis of IPF, FVC between 50 and 90% predicted, predicted range of 30 to 90% of carbon dioxide diffusing capacity, and 6-minute-walk distance of at least 150 m. In the pirfenidone group, the dose was gradually increased to 2,403 mg/d over a 2-week period. The primary efficacy end point in this study was the change from baseline to 52 weeks in the percent predicted FVC in the pirfenidone group. The two key secondary end points were the change from baseline to Week 52 in 6-minute-walk distance and progression-free survival.

Results demonstrate that at Week 52, the proportion of patients who had a decline of 10 percentage points in the predicted FVC or who died was reduced by 47.9% in the pirfenidone group as compared with the placebo group. In addition, at Week 52, a decrease of 50 m or more in the 6-minute-walk distance or death occurred in 72 patients (25.5%) in the pirfenidone group and in 99 patients (35.7%) in the placebo group for a relative reduction of 27.5% in the pirfenidone group. Pirfenidone, as compared with placebo, reduced the relative risk of death or disease progression by 43%, although there was no statistically significant difference in dyspnea or all-cause mortality. The main adverse events were gastrointestinal and skin related.

This study confirmed the promise and efficacy of pirfenidone noted in the prior two CAPACITY trials (2). FVC and 6-minute-walk distances were maintained for longer periods of time in patients on pirfenidone. This study does have limitations: it was conducted on patients with mild to moderate restriction and only took place for 1 year, and results cannot be generalized to patients with more advanced disease or for longer durations of treatment.

References

Harrison MT, et al. Thrombocytosis Is Associated with Increased Short and Long Term Mortality after Exacerbation of Chronic Obstructive Pulmonary Disease: A Role for Antiplatelet Therapy? Thorax (3)

Reviewed by Oleksandr Pistun

Chronic obstructive pulmonary disease (COPD) is a systemic disease, one of the major causes of morbidity and mortality in the developed countries. Increased platelet activation has been reported in acute exacerbations of COPD and even in stable patients...
with COPD. Harrison and colleagues investigated whether thrombocytosis is associated with mortality and also hypothesized that antiplatelet therapy may have a protective role in patients with acute exacerbation of COPD.

In this large cohort study, authors analyzed 1,343 patients who had been previously diagnosed with COPD, were 40 years old or older, and had no airway disease due to other causes. Platelet counts and C-reactive protein levels were measured on admission, and users of aspirin and clopidogrel were recorded as “antiplatelet users.”

Results revealed that 11.7% of the patients had thrombocytosis (defined as > 400 × 10^9 platelets/μl) on admission. A 137% increase in the risk of in-hospital mortality (P = 0.005) and a 53% increase in 1-year mortality (P = 0.03) were found. They also observed that treatment with an antiplatelet drug such as aspirin or clopidogrel was associated with a threefold reduction in the 1-year mortality (P = 0.003) not directly related to a reduction in cardiovascular risk; however, it was not associated with in-hospital mortality rate (P = 0.124). C-reactive protein showed no significant correlation with platelet count (P = 0.5).

This study has some weaknesses: platelet counts were taken only once at admission, making it hard to account for preexisting thrombocytosis, and also it is unclear whether trending platelets during the hospitalization or even after would be useful in helping to draw any conclusions. Compliance with antiplatelet agents on discharge was not followed, which could potentially affect the results of this study.

Despite some limitations, this was the first study examining association of thrombocytosis and mortality after acute exacerbations of COPD and positive effect on mortality of antiplatelet agents. Although it is certainly possible to examine more sophisticated assays involving platelet activation and chemokine release associated with it, platelet count is a very simple and widely available tool, which may help us to identify higher-risk patients. If future randomized, controlled studies find similar benefits of aspirin, without significant contraindications, it appears to be a safe therapeutic choice for the majority of patients with COPD in view of their increased risk of cardiovascular disease. ■

Reference


Grana RA, et al. A Longitudinal Analysis of Electronic Cigarette Use and Smoking Cessation. JAMA (4)

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E-cigarettes are frequently promoted as smoking cessation aids; however, studies demonstrating their efficacy as cessation tools are lacking. Adkison and colleagues demonstrated that although 85% of e-cigarette users reported using them as cessation aids, e-cigarette users did not quit more frequently than nonusers (P = 0.52) (5).

In this study, Grana and colleagues (4) conducted a longitudinal analysis of current U.S. smokers to determine whether e-cigarette use predicted successful quitting or reduced cigarette consumption.

This survey studied recruited smokers in November 2011. Baseline e-cigarette use was measured with a yes-or-no question. Cigarettes used per day, time to first cigarette on awakening (<30 vs. ≥30 min), and intention to quit were measured at baseline and follow-up.

Results showed that significantly more women, younger adults, and individuals with less education used e-cigarettes. At baseline, a greater proportion of e-cigarette users reported smoking their first cigarette less than 30 minutes after waking compared with nonusers (69.0 vs. 57.9%), and baseline e-cigarette use was not significantly associated with greater intention to quit smoking. E-cigarette use at baseline did not significantly predict quitting 1 year later (odds ratio, 0.71; 95% confidence interval, 0.35–1.46; P = 0.35).

Analysis including intent, consumption, and dependence covariates found that intention to quit (P < 0.001) and cigarettes smoked per day (P = 0.02) significantly predicted quit status, whereas past 30-day e-cigarette use did not (P = 0.46). Among participants who reported smoking at both baseline and follow-up, e-cigarette use at baseline was not associated with a change in cigarette consumption (P = 0.25).

This study found that e-cigarette use by smokers was not followed by greater rates of quitting or by reduction in cigarette consumption 1 year later, consistent with the only other known longitudinal population-level study with 1-year follow-up (5). The authors develop a strong argument that regulations should prohibit marketing e-cigarettes as effective smoking cessation devices until claims are supported by scientific evidence; however, larger studies need to be done before making these conclusions. The unregulated nature of e-cigarettes also opens up the possibility of harm, further necessitating regulation. Based in part on this study, the American Medical Association adopted a new policy on e-cigarettes in February 2014, which prohibits their marketing as a smoking cessation tool and calls for disclosures of e-cigarette contents and emissions. ■

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References
