Association between functional improvement and structural changes in quantitative high-resolution CT in ATLAS: a phase 1b study of inhaled pirfenidone in idiopathic pulmonary fibrosis

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Diagnosis

INTRODUCTION

- Functional improvement (FI) is conventionally measured by forced vital capacity (FVC) changes.
- FI is not commonly observed in subjects with idiopathic pulmonary fibrosis (IPF).
- While FI may indicate a response to medication, the correlation between FI and structural change has been underexplored.

AIMS

- This study aimed to associate the FVC changes with quantitative high-resolution computed tomography (HRCT) changes in a cohort of 91 subjects with IPF enrolled in the Phase 1b AP01-002 clinical trial (ATLAS[1]) of 50mg once daily (QD) and 100mg twice daily (BID) of aerosolized pirfenidone.

METHODS

- This phase 1b, randomized, open-label, dose-response trial assessed the safety, tolerability, and efficacy of inhaled pirfenidone (AP01) in IPF.
- Patients with forced vital capacity (FVC) 40%–90% predicted, and intolerant, unwilling, or ineligible for oral pirfenidone or nintedanib were randomized to nebulized AP01 50 mg once per day or 100 mg two times per day for 24 weeks.
- Among 91 participants, 84 had at least 1 monthly FVC follow-up.
- In 70 subjects who underwent baseline and 24-week HRCT scans, 68 had both acceptable HRCT in image quality and available FVC scores.
- FI was defined by any positive changes in the percent predicted FVC (ppFVC) for 24 weeks.
- Quantitative lung fibrosis (QLF) was obtained from HRCT using a machine learning technique.
- Summary statistics and associations were reported to assess the relationship between ppFVC and HRCT changes.

RESULTS

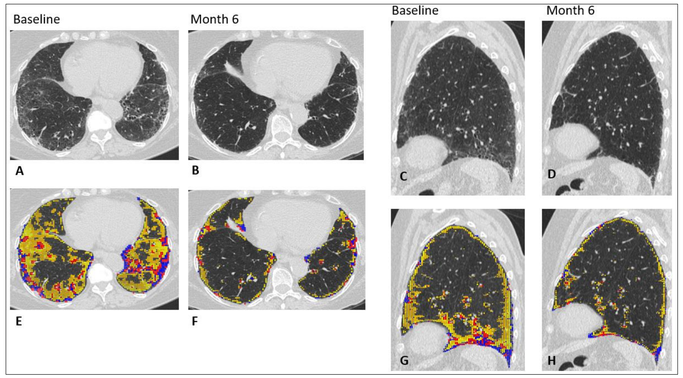

Figure 1: SuperResponder examples. A, B, C, and D: axial and sagittal HRCT images; E, F, G, and H: overlaid quantitative results of the corresponding images of A, B, C, and D. Blue and red dots indicate the results of QLF classification; yellow dots indicate the ground glass. A and C: from the baseline CT. B and D: from the 6-month follow-up CT scans.

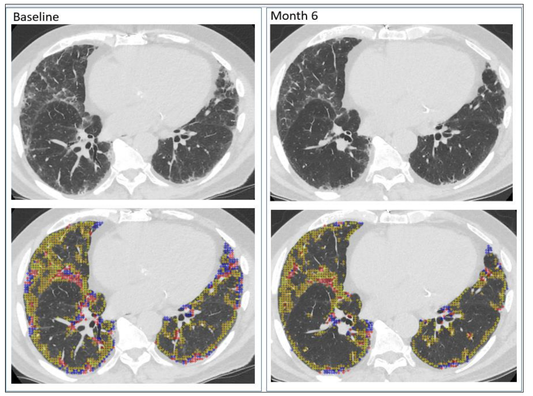

Figure 2: SuperResponder examples. Axial HRCT images and overlaid quantitative results with the blue and red dots indicating the results of QLF classification and the yellow dots indicating the ground glass.

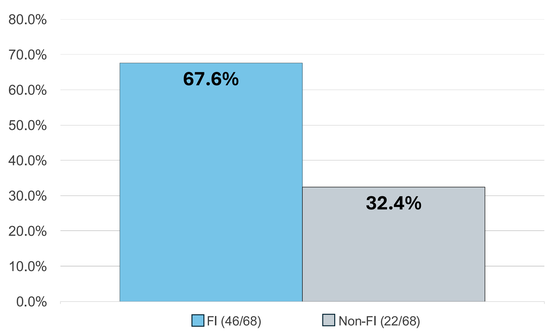

Figure 3: FI versus non-FI (stable or worsening). 46/68 (67.6%) of patients showed functional improvement, whereas 22/68 (32.4%) of patients showed stable or worsening functional improvement on HRCT.

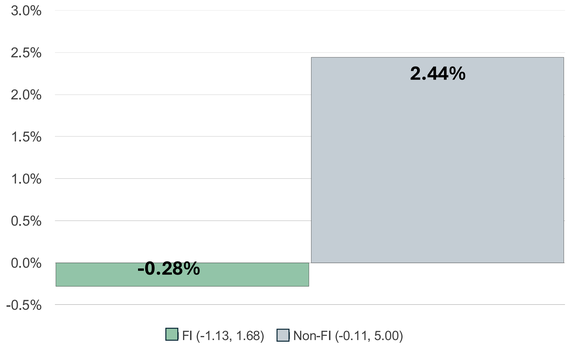

Figure 4: Mean QLF with FI or non-FI. QLF change was -0.28% (-1.13, 1.68) with FI, whereas QLF change was 2.44% (-0.11, 5.00) with non-FI.

RESULTS

- QLF score in whole lung was 8.5% at baseline and 4.9% at 6-month follow-up. QLF volume in whole lung was 258.2 mL at baseline and 154.2 mL at 6-month follow-up. QLF in the left lower lobe reduced from 23.7% (90.6 mL) to 10.6% (45.2 mL) (**Figure 1**).
- QLF score in whole lung was 15.2% at baseline and 11.0% at 6-month follow-up. QLF volume in whole lung was 600 mL at baseline and 449.4 mL at 6-month follow-up (**Figure 2**).
- The distribution of FI in participants was 63.1% (N=53/84), ppFVC 95% confidence interval (CI): 3.36, 5.70%.
- With available HRCT, FI was 67.6% (N=46/68), and non-FI (stable/worsening) was 32.4% (N=22/68) (**Figure 3**).
- Mean QLF changes (95% CI) were -0.28% (-1.13, 1.68) for the FI group and 2.44% (-0.11, 5.00) for the stable/worsening group (**Figure 4**).
- QLF changes from HRCT were significantly correlated with ppFVC changes at Week 24 (rho= -0.34, p=0.0177).

CONCLUSIONS

- FI was frequently observed in 67.6% of subjects at Week 24.
- Both functional and structural changes were correlated with a 24-week course of therapy.
- These data suggest that AP01 (aerosolized pirfenidone) has the potential to reduce lung fibrosis (QLF) in addition to providing beneficial changes in FVC.
- AP01 is currently being investigated in the MIST PPF study, a Phase 2b randomized controlled trial in progressive pulmonary fibrosis.[2]

1. West A et al. *Thorax.* 2023 Sep; 78(9): 882-889. doi: 10.1136/thorax-2022-219391.
2. https://mistppfstudy.com/

PRESENTING AUTHOR DISCLOSURES
Dr. Kim was issued patent 2016-635-1 and is a consultant for Voiant.