TO THE EDITOR: Richeldi et al. (June 9 issue)\(^1\) reported prompt stabilization in lung function in patients with idiopathic pulmonary fibrosis (IPF) who received a preferential phosphodiesterase 4B (PDE4B) inhibitor and a rapid decline in the forced vital capacity (FVC) in patients who received placebo. Over a period of 12 weeks, the mean decline in the FVC was 77.7 ml among patients in the placebo group with background antifibrotic use and 83.8 ml among all patients in the placebo group (Figs. 2 and 3 in their article, and Fig. S5 in the Supplementary Appendix, available with the full text of their article at NEJM.org). These findings should not be dismissed lightly.

A rapid decline in the FVC in patients with IPF is a rare event in clinical practice; the rate of natural decline in FVC is approximately 150 ml over a period of 1 year.\(^2\) The authors postulate the reason for the discrepancy to be that patients enrolled in this trial had more progressive disease than the patients in other trials. However, the demographic and clinical characteristics of the enrolled patients at baseline are similar to those of patients in other IPF trials.

The biologic plausibility of the implied therapeutic effect of the PDE4B inhibitor — by stabilizing, or perhaps even reversing, the fibrosis as early as 2 weeks after the initiation of treatment in patients with IPF — is very low. The results of this trial therefore must be interpreted with caution and raise important questions that temper optimism.

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Dr. Raghu reports receiving fees for serving as an ad hoc discussant from Bristol Myers Squibb and United Therapeutics, receiving consulting fees from Veracyte, receiving fees for reviewing investigator-initiated research grant proposals from Boehringer Ingelheim, providing unpaid consulting services for Biogen, Belvérnon Therapeutics, Blade Therapeutics, Fibrogen, Nitto, Roche/Genentech, and Novartis, serving (unpaid) on a data and safety monitoring board for Avaly, and receiving research grants from the National Institutes of Health. No other potential conflict of interest relevant to this letter was reported.


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TO THE EDITOR: Richeldi et al. found that BI 1015550, an oral PDE4B inhibitor, prevented a decline in lung function as assessed by the FVC in patients with IPF. BI 1015550 stabilized the FVC irrespective of background antifibrotic therapy (either pirfenidone or nintedanib). However, antifibrotics alone appeared to exert a marginal treatment effect over the 12-week trial duration, with a similar median change in the FVC among patients in the placebo group who received background antifibrotic therapy (−59.2 ml) and among those in the placebo group who did not receive such therapy (−81.7 ml). The authors hypothesized that the patients enrolled in this trial may have had more progressive disease than the patients in other trials.\(^1\)\(^4\) They may be in a position to verify this — for instance, by looking at patterns of functional decline in the trial population in the 6 to 12 months before enrollment. The IPF community would benefit enormously from the identification of potential predictors of response to antifibrotic treatment, the lack of which is one of the greatest unmet needs in IPF and in progressive pulmonary fibrosis in general.

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Case 16-2022: A Man with Fevers, Night Sweats, and a Mediastinal Mass

TO THE EDITOR: The report by Fajgenbaum et al. (May 26 issue) describes a patient with idiopathic multicentric Castleman's disease (iMCD) with the TAFRO (thrombocytopenia, anasarca, fever or an elevated C-reactive protein level or both, renal insufficiency or reticulin fibrosis or both, or an elevated C-reactive protein level or both, renal insufficiency or reticulin fibrosis or both, or an elevated C-reactive protein level or both, renal insufficiency or reticulin fibrosis or both, or an elevated C-reactive protein level or both, renal insufficiency or reticulin fibrosis or both).

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