Abstract

Clinical trials that investigate treatments for interstitial lung disease (ILD) regularly apply forced vital capacity (FVC) as primary endpoint. Besides being an important biomarker, FVC is also understood as a surrogate for all-cause mortality. Due to the rarity of the disease and the long time-period required to observe a number of deaths that is sufficient to draw meaningful conclusions from statistical analyses, mortality is impractical as a primary endpoint in clinical trials investigating new treatments. Although the surrogacy of FVC for mortality is biologically plausible and FVC is widely accepted as a surrogate for mortality, statistical evidence that supports the surrogacy assumption is still lacking.

This work aims to apply state-of-the-art methodology for surrogate endpoint evaluation to ILD trial data in order to explore the validity of FVC as an appropriate surrogate for mortality. In particular, two types of statistical modeling approaches were considered: joint models for longitudinal and time-to-event data and Bayesian bivariate meta-analysis.

Joint models for longitudinal and time-to-event data were used to investigate the general relationship between FVC and mortality on the individual patient level and the models were fitted on pooled data from six ILD trials that investigated the effect of the drug nintedanib. To consider the correlation between the treatment effects on FVC and mortality, Bayesian approaches to bivariate meta-analysis were applied and the models were fitted using the estimated treatment effects from the six nitedanib trials and two pirfenidone trials. The models were fitted using different effect estimates from the same trials and different approaches for handling the within-study correlations, including a bootstrap procedure, to assess the sensitivity of the results regarding these aspects.

The results of the joint modeling approach confirmed surrogacy on the individual patient level. Using the meta-analytic approach, a definite correlation of the treatment effects could not be demonstrated. However, refitting the meta-analytic models when additional data is available appears sensible to further investigate the validity of FVC as a surrogate endpoint for mortality.

Key words: Surrogate endpoint evaluation, interstitial Lung disease, joint models, longitudinal data, time-to-event data, meta-analysis, Bayesian statistics, bootstrap.