How to improve statistical power in a trial with SCA2 patients

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Résumé

ABSTRACT

Background and objectives

ATRIL study showed that riluzole did not improve clinical outcomes (Coarelli et al., 2022). SARA scores showed indeed a median increase (ie, worsening) of 0.5 points (IQR –1.5;1.5) in the riluzole group versus 0.3 points (–1.0;2.5) in the placebo group (p=0.70). Our objective is to use recent advancements in statistical methodologies to improve the trial analysis.

Methods

SCA2 patients from different cohorts of the US and European centers were selected in a longitudinal dataset (EUROSCA, SPATAX, CRC-SCA, RISCA), to train a progression model capturing the natural disease development in untreated patients (Disease Course Mapping using Leaspy python library). Based on the prognostic score generated by this model, we applied prognostic covariate adjustment (PROCOVA) and prediction-powered inference (PPI++) to improve the power of the ATRIL clinical trial, involving both treated and placebo SCA2 patients. The PROCOVA method incorporates the prognostic score as a covariate in an analysis of covariance (ANCOVA), where the change in SARA score is regressed on both the treatment indicator and the prognostic score. The PPI++ method leverages the prognostic score to offer an unbiased comparison between the observed SARA score evolution in treated patients and the predicted SARA score evolution if they hadn't been treated.

Results

Looking at the correlation between the predicted and real progression of the SARA score for one year, our progression model accurately forecasted prognostic scores for SCA2 patients,

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providing insights into disease progression trajectories. The estimator for the treatment effect had a lower variance using the PPI+++ (0.346) and prognostic covariate adjustment methods (0.385) compared to the classical variance (0.407), allowing a gain in power for the treatment comparison. Incorporating the prognostic score among the covariates could allow to reduce the sample size of 13% (5 patients), while maintaining the same power.

Discussion

Prognostic scores provide a more robust alternative to simple matching techniques, such as matching-adjusted indirect comparison (MAIC), which focuses on adjusting baseline characteristics between treatment groups without using prognostic scores. By integrating prognostic scores, our study addresses the dual challenge of identifying the optimal longitudinal model for predicting disease progression and improving the conclusions of the ATRIL trial through advanced statistical methods. These methods incorporate natural disease progression predictions to reduce confidence intervals, enhance statistical power, and decrease the required sample size for the trial, all while maintaining result validity. This approach has the potential to refine treatment efficacy assessments and support more informed clinical decisions in ataxia management.