Modeling different progression endpoints and identifying prognostic factors in early Parkinson’s disease

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Objectives: Parkinson’s disease (PD) is an heterogeneous disease in terms of genetics, pathology, predominant clinical symptom (tremor-predominant, postural instability – gait disorder predominant) and disease progression measured with clinical scales such as the Unified Parkinson Disease Rating Scale (MDS-UPDRS) and dopamine transporter imaging (DAT-SPECT SBR). Longitudinal data up to 24 months, from PPMI (the Parkinson's Progression Marker Initiative) [1], were analyzed with the aim to identify the most informative markers, their correlations and effect of the different covariates on disease progression. Identifying early-stage patient subgroups with different progression rates and factors influencing the progression is of key importance for disease understanding and proof-of-concept (PoC) study planning for compounds with putative disease modification effect.

Methods: MDS-UPDRS/UPDRS III were described using a combination of exponential decay and linear progression models. DAT-SBR data, collected in different brain regions, were simultaneously described by an exponential model with a unique progression rate, including correlations between the rate and baseline. Covariate analysis was performed on both models. A set of covariates and the shape of the trajectory of the target endpoint were used for computing the probability to be a fast/slow disease progressor. Sample size was determined according to data and model predicted values.

Results: Despite patient’s stratification based on the most relevant covariates, the between subjects variabilities in the endpoints were high, justifying the necessity to properly power any PoC study. A disease-modification trial in early PD using MDS-UPDRS/UPDRS III as primary endpoint would require more subjects than a trial using DAT imaging. An early read-out of the study outcomes can be used as a criterion for adapting the study design (including discontinuation for inefficacy). Based on data and on model prediction values, the correlations between the different endpoints were evaluated.

Conclusions: The proposed model based approach is expected to facilitate and improve the PoC study design, its execution and evaluation of clinical data in early PD.

References: [1] www/ppmi-info.org