THE PLACEBO GROUP SIMULATION APPROACH (PGSA): REPLACING PLACEBO IN LONG-TERM TRIALS WITH PRE-SYMPTOMATIC AD PATIENTS

R. Spiegel, M. Berres, A.R. Miserez, A.U. Monsch

Memory Clinic, Geriatric University Hospital, University of Basel, Basel, Switzerland

Novel compounds with potential to attenuate or stop the progression of Alzheimer disease (AD) from its pre-symptomatic stages to dementia are being or will soon be tested in man. The conventional study design is the randomized, placebo-controlled clinical trial (RCCT), which implies that a high proportion of patients will receive placebo treatment for 18 months or longer. However, it is ethically problematic to expose patients with pre-symptomatic AD, who by definition run a high risk of developing dementia, to extended placebo treatment. In an attempt to realize an ethically acceptable and scientifically sound alternative to RCCT designs, we have developed mathematical models to reliably forecast clinically relevant endpoints and disease trajectories of pre-symptomatic AD patient groups. Our models make use of anamnestic, biological and neuropsychological measures that are routinely established at baseline of every study. Model-based forecasted endpoints and trajectories constitute the background - the “simulated placebo group” - against which potential drug effects can be contrasted.

We will present first results to demonstrate that empirically established and mathematically modelled endpoints and disease trajectories do show high concordance in large samples of pre-symptomatic AD patients. We posit that the PGSA (Placebo Group Simulation Approach) will help to reduce ethically problematic long-term RCCTs in conditions characterized (i) by a fatal outcome and (ii) by a well-known, quantifiable disease course.