Washout of treatment effects is essential for distinguishing short (symptomatic) and long-term (disease modifying) treatment effects from natural disease progression

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Objective: To compare the power of washout and delayed start designs for distinguishing short (symptomatic) and long term (disease modifying) effects of drug treatments in slowly progressive diseases using disease progression modeling.

Introduction: Ideally, treatment should slow down or even reverse the progression of a slowly progressive disease, such as Parkinson’s and Alzheimer Disease. A treatment effect with a short onset of action, which is reversible after cessation of treatment is referred to as ‘symptomatic’. A treatment effect is called ‘protective’ or ‘disease modifying’ when the onset of the treatment effect is slow and persists after treatment effects are thought to have washed out [1]. For estimating the actual treatment effect it is, therefore, essential to distinguish the time course of treatment effects from those due to natural disease progression [1]. In addition, the trial design should allow for distinguishing short-term and long-term treatment effects from natural disease progression.

Over the years, three trial designs have been proposed to distinguish symptomatic from protective effects: 1) Parallel group design (placebo and active treatment) 2) Washout design with follow-up after treatment withdrawal 3) Delayed start design in which one of the groups receives placebo treatment first for a period of say 6 months followed by active treatment for the same period, whereas another group receives active treatment immediately and continues for 12 months.

The designs are illustrated using Parkinson’s disease as an example in Figure 1. The change in the unified Parkinson’s disease rating scale (UPDRS) over time for a drug with an effect on the slope and offset of the natural disease progress is shown for the 3 different designs. The analysis of these designs requires making explicit assumptions. In the wash-out design any symptomatic treatment effect should be completely washed-out to claim that a difference between the placebo and active treatment group at the end of the wash-out period is due to a disease modifying effect. The claim of disease modifying effects on the basis of differences between the delayed and immediate start groups in the delayed start design requires the assumption of complete wash-in of any symptomatic effect during the delayed start period [2]. However, testing the validity of these assumptions is difficult. In the case of slow washout of the symptomatic effect, the washout period needs to be very long. It is likely that this will be associated with considerable patient dropout, thereby reducing the statistical power. On the other hand, a slow onset of a symptomatic effect requires a long trial to assure complete wash-in of this effect at the end of the trial. However, when analyzing the data with a combined disease progression model and delayed onset pharmacodynamic model, characterizing the change in disease status over time in addition to the time-course of the treatment effects, these assumptions are explicitly taken into consideration in the analysis [1].

Methods: The change in UPDRS over time was simulated for a hypothetical drug showing an effect size comparable to that of deprenyl [2] of -6 units/year with a washout and delayed start design. It was assumed that 50% of this effect was due to disease modifying effects and the other 50% due to a symptomatic effect at 16.6 months. A disease progression model with linear disease progression in untreated patients was used assuming immediate and delayed onset (effect compartment model) of the disease modifying and symptomatic effect respectively [2]. Drop-out was simulated assuming that the drop-out hazard increased linearly with disease status. Different drop-out scenarios were evaluated resulting in 30, 40 or 70% drop-out after the end of the trial (16.6 months). Both designs included 2 groups of 500 subjects. The washout design included a placebo and active dose group. In the delayed start design, one group started on placebo and switched to an active dose after 6 months, whereas the other group received active treatment immediately. The washout period in the washout design was 3 months. Optimal sampling times were obtained from WinPOPT [3]. The simulated data using the combined effect model were analyzed with the true model and two alternative models with only a slope or offset effect
respectively. Estimation was performed using NONMEM Version VI 1.2 with the FOCE estimation method. The accuracy and precision in the estimated parameter values of the true model were compared in addition to the power to distinguish the true model from the alternative models. The power was derived from the number of times that the true model was significantly better compared to the alternative models using a likelihood ratio test.

Results: The effect size for the disease modifying effect was estimated with better accuracy and precision on the washout data compared to the delayed start data when an equilibrium half-life of 14 days for the symptomatic effect was assumed. In addition, the power to distinguish the true combined effect from a pure symptomatic effect was remarkably lower for the delayed start design, which was about 50% of the power of the wash-out design, which was greater than 90%. However, when an equilibrium half-life of 90 days was assumed, this power dropped below 50% for the wash-out design also. On the other hand, the parameters could be estimated with comparable accuracy and precision. Drop-out appeared to have a greater impact on the statistical power compared to the accuracy and precision of the parameter estimates. For a drug with an equilibrium half-life of 14 days the power for the washout design is still greater than 80% for 40% dropout, but drops to about 50% in case of extreme dropout of 70% at 16.6 months.

Conclusions: Washout of treatment effects provides crucial information for distinguishing symptomatic from disease modifying effects with a model-based analysis. Despite higher expected dropout in a trial in which patients will be withdrawn from active treatment, the statistical power of a wash-out design for estimating the true treatment effect size is greater compared to a delayed start design. Both designs fail to separate a very slow onset symptomatic effect from a disease modifying effect.

References:

