Joint Parametric Models For Best Visual Acuity Score and Central Retinal Thickness for Patients with Age-Related Macular Degeneration

Anna Georgieva Kondic, Witold Wiecek, Certara

Background: Age-related macular degeneration (AMD) is the leading cause of severe and irreversible visual loss world-wide with effect on quality of life of affected individuals and large economic burden on the health care systems. Particularly dangerous is the wet AMD (wAMD), which occurs when blood vessels grow abnormally in the macula (part of the retina) and eventually produce scarring, which in turn obstructs vision. Vascular endothelial growth factor (VEGF) is an important pathophysiological factor in neovascular wAMD. The wide introduction of anti-VEGFs therapies has led to an overwhelming improvement in treatment outcomes in patients affected by wAMD, allowing recovery and maintenance of visual function in the vast majority of patients. However, these drugs are not cheap and also they present a management problem in large populations. The burden of disease has turned into a burden of care with a dissociation of scientific advances and real-world clinical performance.

Simultaneously, innovations in diagnostic technologies, such as optical coherence tomography (OCT) can aid early disease detection and efficient therapeutic follow-up. However, definite link between morphologic parameters and wAMD endpoints are still lacking, and valid biomarkers have yet to be identified to provide a practical base for disease management.

Two of the more traditional clinical endpoints in neo-vascular wAMD are Best Corrected Visual Acuity Score (0-100) and Central Sub-Field (Retinal) Thickness (measured in microns). They are both continuous quantities, being measured at the time of dose (ocular injection) administration or at unscheduled visits (usually 3 doses every 4 weeks, followed by a less frequent maintenance phase). The correlation between these two quantities is weak over the entire course of treatment but will depend on time. Pharmacometric models (linking drug exposure in the eye to the response variable) exist for BCVA (Mulyakov et

al), but this is not the case for CSFT, where the patterns in some patients are less smooth and exhibit oscillations.

Problem at hand:

Our goal is to create models that are computationally efficient and capture dose administration regimen and potentially dependencies on patient specific characteristics. A crucial first step is to use first principles and select an appropriate structural model for each of BCVA and CSFT that is consistent with the observed data. In this exercise, we would like use some representative curves to illustrate where the challenges and nonlinearities are. In particular, we would like to understand:

1) What is the minimum number of parameters that is needed to accurately describe the curves?
2) Can the subjects be grouped in a few classes, depending on the behavior of the curves?
3) Is there a way to predict the pattern for how the occurrence of these oscillations, as well as their amplitude?
4) How much of the patterns can be described with a single covariate, namely the time since last dose?