APBD Heterogeneity: The Case of the Triheptanoin Trial

by Larry Schwartz, January 2018

Introduction

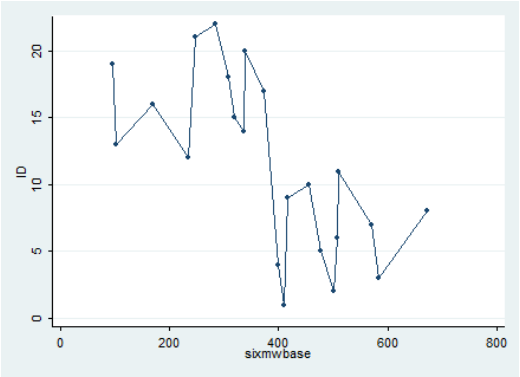
According to a 2012 FDA/NIH workshop, patients with rare diseases have highly heterogeneous conditions.[1] Patients with the Adult Polyglucosan Body Disease (APBD) are no exception----In the results for the Triheptanoin Phase 2 clinical trial for this rare disease, Dr. Raphael Schiffmann, the PI, states, "This study…emphasizes the difficulty of conducting trials…with a wide clinical heterogeneity." [2]

In this brief note, I quantify the APBD heterogeneity problem from the baseline six-minute walks recorded for this Triheptanoin trial. In a follow-on paper, I plan to develop relatively homogeneous sub-classes for this trial with the well-established statistical technique of cluster analysis. The clustering process used in this trial would serve as a template to similarly develop such sub-classes for future APBD trials.[3]

Wide APBD Heterogeneity

Graph 1 illustrates the heterogeneity for the Triheptanoin Phase 2 trial for APBD. On the vertical axis is the ID numbers assigned to each of its 22 APBD participants. On the horizontal axis is the baseline for the six-minute walk, in meters (the primary endpoint in this trial). Visually, there seems to be a great deal of variation in six-minute walking among the 22 patients that participated in this trial.

Graph 1. Baseline Six Minute Walk for Trial Participants



[1] *NIH and FDA, Workshop on Natural History Studies of Rare Diseases: Summary*, NIH Campus, May 2012.

[2] Schiffmann, R. and others, "*A double-blind, placebo-controlled trial of triheptanoin in adult polyglucosan body disease and open-label, long-term outcome*," Journal of Inherited Metabolic Disease, 6 November 2017. This publication provided partial supplementary data to the public online, and I use these data for this brief note.

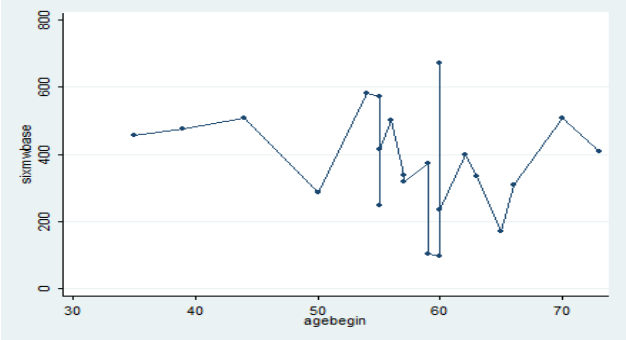
[3] In order to perform the cluster analysis, we have requested that Dr. Schiffmann provide the full de-identified baseline data for the Triheptanoin trial. Our request was granted and we await receipt of these data.

In statistical terms, the mean for the baseline six-minute walks was 377 meters, with a standard deviation of 153 meters (spread around the mean). For summary purposes, the coefficient of variation (CV) takes the standard deviation and normalizes it with the mean, useful for comparing results to other relevant areas. The CV for this APBD trial is 41 percent (153/377) ----much higher than what is acceptable for *inte*r-assay lab work (15 percent) or *intra*-assay lab work (10 percent).[4] In short, APBD seems to be a highly heterogeneous condition.

But surely there is a smooth relationship between the ages of APBD patients (at time of consent to participate in the trial) and the six-minute walk----one that could help break down the APBD heterogeneity. After all, the APBD literature documents a progression of median ages for this disease: 51 years old for the onset of neurogenic bladder[5], 60 for cane use[6], and 68 for the wheel chair[7]; with a median lifespan of 70 years[8].

To investigate the walking-age relationship, Graph 2 shows the six-minute walk on the vertical axis and the age of the trial participants on the horizontal axis.[9] Visually, there does not seem to be a smooth change in the six-minute walk with the ages of the trial participants.

Graph 2. Baseline Six-Minute Walk by Age of Participants



Statistically, the correlation between the baseline six-minute walks and participant ages is minus 0.23---negative, as expected, but weak. Further, APBD heterogeneity again is made abundantly clear especially with three trial participants aged 60: Incredibly, their six-minute walking distances varied from a low of 95 meters, to an intermediate level of 235 meters, to a high of 672 meters. Also, the trial participants aged 35 and 39 do not have the longest six-minute walks, as you might expect; some participants in their 40s and 50s, and especially at age 60, have longer walking distances.

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[4] Steven, "*How to Calculate the Coefficients of Variation*, "Top Tip Bio, April 5, 2017.
Salimetrics, "*Inter- and Intra Assay Coefficients of Variation,*" about 2010.

[5] Fanny M. and others, "*Adult Polyglucosan Body Disease: Natural History and Key Magnetic Resonance Imaging Findings*," Annals of Neurology, September 2012.

[6] Hellman, M.A. and others, *"Frequent Misdiagnosis of Adult Polyglucosan Body Disease*," Journal of Neurology, July 2015.

[7] Same as footnote 6.

[8] Same as footnote 6.

[9] Note that the Triheptanoin Phase 2 clinical trial for APBD excluded those in a wheel chair or wheel-chair bound. Consequently, the APBD heterogeneity shown in this paper may be an underestimate of the true heterogeneity for the APBD condition.

Promise of Cluster Analysis

But it is possible to break down such wide heterogeneity into relatively homogeneous sub-classes. In biology, genetics and medicine in general (also social sciences, marketing, archaeology, taxonomy, and other disciplines), the multivariate statistical technique of cluster analysis is commonly used for this purpose.[10] Preliminarily, I have applied cluster analysis to the baseline six-minute walks of this trial and found encouraging results in reducing its heterogeneity; however, I await the receipt of the full baseline data from Dr. Schiffman to complete this work.

A visual inspection of Graph 1 provides a hint that there may be two distinct clusters of APBD patients. One cluster could be for mild cases of APBD where six-minute-walking distances are at least 400 meters. The other cluster could be for more severe cases of APBD where six-minute-walking distances are under 400 meters. However, a formal cluster analysis may yield different results.

The clustering process to reduce APBD heterogeneity in this trial could serve as a template for future APBD trials. It would not matter which primary endpoint is selected for a future APBD trial---six-minute walk, ALS Functional Rating Scale, or some other measure---to apply the clustering template and provide relatively homogeneous sub-classes for a future trial.

In turn, the resultant relatively homogeneous sub-classes can be used to populate separate arms for clinical trials----permitting tests for efficacy not only on a global basis, but also on an individual sub-class basis. Sometimes a treatment is more effective if applied earlier to the patient rather than later, but the global basis cannot (legitimately) uncover this distinction whereas the sub-class basis can.

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[10] **Peters, J.B. and others, "*Integral Health Status-Based Cluster Analysis in Moderate–Severe COPD Patients Identifies Three Clinical Phenotypes: Relevant for Treatment as Usual and Pulmonary Rehabilitation*," International Journal of Behavioral Medicine, 2017.**

Axén, I. and others, "*Clustering patients on the basis of their individual course of low back pain over a six-month period*," BMC Musculoskeletal Disorders, *17 May 2011*.

Mulroy, S. and others, *"Use of cluster analysis for gait pattern classification of patients in the early and late recovery phases following stroke*," Gait & Posture, August 2003.