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Methodological Insights for Randomized Clinical Trials of Retinitis Pigmentosa:

Lessons Learned From a Trial of Valproic Acid

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Retinitis pigmentosa (RP) is a genetically heterogeneous group of photoreceptor degenerations for which no treatments exist. In this issue of *JAMA Ophthalmology*, Birch and colleagues¹ report on the repurposing of oral valproic acid as a potential treatment for autosomal dominant RP. The authors found that valproic acid made the progression of isopter III4e visual field deteriorate faster than those in the placebo group. Although at first glance, one might think that there is little to say in commenting on a study that did not have a successful primary outcome; however, we submit that there is much to be learned from this article.

The criterion standard, of course, for establishing efficacy for any treatment is the randomized, double-masked, placebo-controlled clinical trial. However, retinal degenerations such as RP pose several challenges when trying to establish this level of proof. First, RP and other mendelian retinal degenerations are rare, affecting 200 000 (80 000 with RP) individuals in the United States.^{2,3} Second, much of the time, these diseases are slowly progressive, making the following of progression a challenge; this is particularly true in autosomal dominant RP, at least relative to recessive and X-linked forms. Third, even in relatively genetically homogeneous populations such as those with Stargardt disease (*ABCA4* retinopathy), the rate of progression is quite variable.

The process of conducting a multicenter trial of this magnitude for a rare disease such as RP is itself educational. As the authors point out, “this study brings to light the key methodologic considerations that should be applied to the rigorous evaluations of treatments for these conditions.”¹ This study began in 2011 and required approximately 3.5 years to reach full enrollment. The primary outcome variable chosen (change in isopter III4e visual field area) was based on the best evidence available at the time. Fast-forward to 2018: collaborative, multicenter groups such as the ProgStar Consortium are systematically characterizing patients’ natural history of progression in anticipation of therapeutic trials.⁴ Looking for a slowing of progression is likely a much more achievable goal than improvement in visual function. The experience with *RPE65* gene replacement

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therapy in Leber congenital amaurosis is likely to be more an exception, rather than a rule, in the near term. Advances in ophthalmic imaging, such as optical coherence tomography, autofluorescence and adaptive optics, as well as, importantly, a better understanding of the variability of these and psychophysical methods,⁵ have changed the landscape of clinical outcome variables. For example, in 2013, Birch et al⁶ demonstrated that loss of the ellipsoid zone band on optical coherence tomography in RP is a highly reproducible, quantitative measure of RP progression during a comparatively brief period. Even something as straightforward as a reanalysis of this study's raw data using more modern concepts of progression, such as a log or square root transform of visual field area, may be enlightening.⁷ This study and similar studies such as ProgStar⁴ have demonstrated that clinical and natural history trials of rare inherited retinal diseases are possible with the collaboration of many eminent retinal degeneration groups. We fully anticipate that the next such trial we read in the pages of *JAMA Ophthalmology* will be accomplished in shorter order and using tests with better test-retest parameters.

Second, the authors found that valproic acid, a US Food and Drug Administration–approved drug with significant potential for major adverse effects, made the progression of stimulus isopter III4e visual field deteriorate faster than those in the placebo group. If the authors had not done this study and the patient population was left with the results of the published, positive-finding pilot trial, we anticipate that many more patients would have gone on to use this medication off-label, likely with significant potential risk. On a related note, had the authors set the V4e isopter as their primary outcome variable, this study would have reported a positive result with approximately the same level of statistical significance.

Last, this article serves as a challenge for how we might think about future randomized clinical trials. In our experience at the National Eye Institute with *ABCA4* retinopathy, we have found that, despite all having mutations in the same gene, patients vary greatly in their rates of progression. However, when following specific imaging parameters, most patients progress in a linear fashion. Therefore, in the presence of robust natural history data, each patient could serve as their own control, with the change in the rate-of-change (slope), pretreatment, and posttreatment, becoming the outcome measure. Although a control group assigned at random will usually be necessary for phase 3 studies, this “within patient” paradigm can reduce the sample size and duration of phase 2 studies, which is especially important in assessing new treatments for rare diseases.

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