Learning to walk: Challenges for spinal muscular atrophy clinical trials

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Editorial

Learning to walk

Challenges for spinal muscular atrophy clinical trials

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Spinal muscular atrophy (SMA) is a genetically determined neuronopathy and usually presents in childhood. SMA has a broad range of phenotypes: severe early infancy onset (type I, Werdnig-Hoffman disease, non-sitters), later infancy onset, intermediate variety (type II, sitters, non-walkers), and childhood to adulthood onset (type III, Kugelberg-Welander, walkers).[1,2] In addition to progressive limb and truncal weakness, dysphagia, aspiration, and respiratory insufficiency are predictable life-threatening comorbidities of the infantile type I and II forms.[3] As yet, no effective drug therapy has been found for human SMA.

Advances in molecular genetics led to the discovery of the causative mutation in the Survival Motor Neuron *(SMN) 1* gene and elucidation of the rescue of an otherwise lethal condition by a nearly identical homologue gene, *SMN2*.[4] The number of copies of this *SMN2* gene is inversely associated with disease severity, and this gene dosing observation has led to treatment strategies targeting SMN2.[5] These strategies for SMA include induction of SMN2 gene expression, modulation of splicing of SMN2-derived transcripts, and stabilization of SMN protein.[6] Each approach will in theory generate more SMN protein and might ameliorate the accelerated motor neuron loss and progressive muscular atrophy. In vitro or animal model studies of valproate, phenylbutyrate, and hydroxyurea have demonstrated promising results and each is now in clinical trials.[7]

Clinical trials in SMA present challenges at several levels.[8] Being a neuromuscular disorder, the primary outcome measure should be a motor measure that is clinically meaningful and developmentally age-appropriate. In older children, measures of strength, and motor function scales have been used in neuromuscular trials, but both have limitations. Recent efforts to explore these measures in SMA have been fruitful, but no consensus has been reached as yet among the SMA study groups. Secondary outcome measures should include clinically meaningful measures and biomarkers. Potential biomarkers in SMA include measuring the amount and ratio of full-length and truncated *SMN2* RNA transcripts and the amount of SMN protein from peripheral blood leukocytes or in patient fibroblast culture. Technical issues with collecting, processing, and assaying patient samples remain, but much progress has been made recently. Recruitment from a small pool of eligible subjects, retention of medically fragile patients, and promoting a placebo-controlled blinded study with good drug compliance are all significant issues in SMA clinical trials. Having energized and focused patient advocacy groups endorsing controlled trials can assist with many of these obstacles and serve as much more than a source of funding.

In this issue of *Neurology*, Mercuri et al.[9] report a clinical trial of phenylbutyrate (PB) in SMA type II. Although there was no benefit of the drug, the information gained is important in planning future trials: the 107 participants in this multicenter trial received PB intermittently for 13 weeks or matching placebo. The change in the Hammersmith Motor Function Scale (HMFS) over 13 weeks was the primary outcome. Muscle strength and pulmonary measures were secondary outcomes. The study demonstrates the feasibility of recruiting 107 patients over 9 months into a placebo-controlled trial. Retention, however, was a challenge, as 13 of 107 patients did not complete the relatively short treatment period of 13 weeks, due to parental refusal, poor medication tolerability, or adverse effects. As a result of incomplete assessments or protocol violations, data on 17 of 107 patients had to be imputed under the intention to treat principle. This indicates the need for educating patients at enrollment on the importance of study completion, even when the study

See also page 51

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drug is discontinued, and independent of any perceived benefit.

The authors suggest that the unexpected improvement in both the PB and placebo group is due to a placebo effect. This effect was probably magnified by the short study duration as it is likely transient. While a placebo effect should not alter the conclusions of well-blinded, placebo-controlled trials such as the current one, it could reduce the power of a blinded trial, or give a false positive result in an open label trial.

Mercuri et al. have confirmed that motor function assessments are feasible as the primary outcome in SMA trials. Although PB was not beneficial under the conditions of this study, the authors discuss that a longer treatment period should be tested. Rescuing neurons to measurably restore motor function may require an observation period beyond 13 weeks. Also, an alternative dosage or regimen might have been more effective. A phase I study addressing some of the issues related to dose and regimen is under way in North America.[10]

This study underscores the importance of subject retention in such trials. It shows that controlled trials like the one conducted by Mercuri et al. are needed to evaluate drug efficacy in SMA because of the placebo effect that would increase the likelihood of falsely concluding benefit from short-term open label trials. The study gives hope that with enhanced investigator collaboration, and increasing education of the SMA patient community, a well controlled multicenter trial will soon lead to the long-awaited first success in finding an effective drug treatment for SMA. We learn to walk before we run.

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