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Mexiletine for Treatment of Myotonia:

A Trial Triumph for Rare Disease Networks

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Patients with nondystrophic myotonias typically have myotonia as an isolated symptom, without muscular wasting, although the patient's myotonia may be associated with muscle weakness and fatigue or transient attacks of paralysis. Episodes of myotonia may be triggered by cold (paramyotonia congenita), potassium (potassium aggravated myotonia), or exercise (Thompson and Becker myotonia). Most cases of nondys-trophic myotonia are caused by mutations in 2 skeletal muscle ion channels: the voltage-sensitive sodium channel responsible for carrying the action potential (*SCN4A*) and the chloride channel responsible for maintaining the resting membrane potential (*CLCN1*).[1]

In this issue of JAMA, Statland and colleagues[2] report the results of a randomized, placebo-controlled, crossover trial of mexiletine involving patients with nondystrophic myotonia, with a focus on improvement of reports of stiffness. Patients were randomized to 4 weeks of either mexiletine or placebo, a week of washout, and then crossover to the other agent. Mexiletine is a well-characterized sodium channel blocker,[3] and it has been prescribed off-label to treat myotonia for many years. However, clinical trials of this drug for this indication have been lacking, despite improvements in understanding of the genetic basis for these disorders.

Why is this report important? First, this is a well-designed trial of orphan diseases with genetic and clinical heterogeneity, and such trials are difficult to conduct. The rarity of these disorders makes recruitment for therapeutic trials a challenge, whereas the heterogeneity of these disorders makes targeting specific underlying disease mechanisms and specific clinical manifestations problematic. The Consortium for Clinical Investigation of Neurologic Chan-nelopathies (CCINC) was established with the support of the National Institutes of Health

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Hoffman reported serving as a board member, holding founder shares in, and owning stock in Revera-Gen Biopharma; receiving royalties on a patent from Boston Children's Hospital; and receiving grants from the National Institutes of Health, Muscular Dystrophy Association, and the Foundation to Eradicate Duchenne. Dr Kaminski reported receiving fees from legal firms for expert testimony; and receiving grants from the National Institutes of Health and MG Foundation of America.

(NIH) to bring together patients and investigators and to address these challenges. This trial demonstrates the ability of robust clinical research consortia to conduct well-controlled clinical trials of rare disorders.

Another triumph of this study was its rapid completion. Fifty-nine patients were randomized and the study was completed in 28 months; this is noteworthy for a group of diseases with a worldwide prevalence of 1 per 100 000.[4] Although trial performance ultimately depends on patient recruitment, patient adherence and contractual issues, especially for international trials, can slow the start of trials and can adversely influence their successful completion.[5,6] This trial, which involved 7 sites in 4 countries, appears to have overcome these obstacles. The successful execution of this trial should be attributed to the consortium that provided a population of patients closely associated with each tertiary care facility and an established infrastructure, which included common data elements, validated outcome measures, and expertise in the specific disorders.

Another feature of this trial was the use of an innovative patient-centered primary outcome measure; patients reported stiffness via an interactive voice response (IVR) system.[7] The IVR system is a unique medium that allows patients to call and respond to validated assessments of their symptom severity. The system eliminated need for cumbersome paper diaries, which are burdensome for most participants and research coordinators. The IVR system also provided a clear time stamp for documentation, and it may have improved adherence due to reminder calls. Patient participation with calls to the IVR at the primary end point time of 3 to 4 weeks was excellent and pill counts also indicated greater than 90% adherence. Patients also completed secondary outcome measurement that included electrophysiological testing.

Most important, the drug worked. The investigators found that mexiletine improved stiffness as assessed by the IVR, and this result was supported by electromyography and handgrip testing. The critical point is whether these statistically significant improvements truly mean that patients' lives are better. Statland et al[2] describe effect sizes for outcome measures that were greater than 0.5 and some greater than 0.8, indicating a moderate to large response to treatment. This would translate to a treatment effect that would suggest improvements in stiffness for mexiletine compared with placebo. This is consistent with a clinically meaningful outcome.[8] Mexiletine was well tolerated, with the caveat that patients with a history of cardiac disease were excluded. Patients with chloride channel mutations experienced greater reduction in handgrip myotonia than those with sodium channel mutations.

There are also limitations to the study. The trial duration was too short (4 weeks of treatment) to be confident of the long-lasting effects of mexiletine and the trial was too small and too brief for determination of safety in these conditions. Mexiletine is already in common use by clinicians for the treatment of myotonia,[4,9] and the trial may bolster its continued off-label use. Also, the patients in the trial were probably quite heterogeneous in a number of respects, and this may have contributed to the significant differences in both baseline myotonia and response to the drug between the period 1 and period 2 crossover

groups. Specifically, a substantial subset of patients reported infrequent episodes of myotonia at baseline, making it challenging to detect drug-related improvements.

In addition, the nondystrophic myotonias show a wide range of symptoms based on the specific gene (*SCN4A* or *CLCN1*), and the specific mutation within each gene, yet only symptoms and signs related to myotonia were studied by Statland et al. Mexiletine, a sodium channel blocker, targets the primary defect in sodium channelopathies (excessive activation of the sodium channel SCN4A channel protein)[10] but targets more downstream cell pathophysiology in the chloride channel, adding cellular heterogeneity to the genetic and allelic heterogeneity. A future approach may involve a more targeted trial, in which inclusion criteria would be limited to a single mutation of a single gene. However, at this point such an approach is not feasible, considering that symptoms vary widely even within a single family segregating the same mutation in the same gene,[11] and each individual mutation is so rare as to make adequate recruitment all but impossible.

The study by Statland et al[2] provides important information that should help inform the treatment of patients with myotonia. The success of this trial should encourage the CCINC group to take the lead with larger phase 3 trials. Even more exciting would be development of novel agents that can produce therapeutic benefit with much greater effect sizes. Most important, the NIH, industry, and patient advocacy groups should attempt to replicate the success of the CCINC through establishment of more clinical research consortia focused on rare disorders.

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