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COMMENTARY

Targeting the Neuromuscular Junction in ALS

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Over the past 10 years, our understanding of the genetic basis for amyotrophic lateral sclerosis (ALS) has grown enormously. From these studies, it is clear that defects in multiple cellular processes can cause the disease. Although much effort is directed towards developing therapies that target specific processes associated with a genetic mutation, the therapies that may translate best to sporadic forms of the disease may be drugs with the potential to mitigate pathogenic processes downstream of the primary cellular defect, which remains elusive for sporadic ALS. One such critical process in ALS may be preservation of the neuromuscular junction [1].

In the current issue, Pozzi et al. present data on the long-term administration of pimozide in the standard G93A mutant superoxide dismutase 1 (SOD1) mouse model of ALS and a more recently developed model that expresses a mutant form of human TAR DNA-binding protein 43 (TDP43) [2]. Pimozide is a D2 dopamine receptor antagonist that is approved by the US Food and Drug Administration for schizophrenia, but is also used for two hyperkinetic disorders, chorea and tics. Interestingly, recent studies have found a potential link of neuropsychiatric disease and ALS [3]. Pimozide was identified initially as a potential therapy in a *Caenorhabditis elegans* model that displays locomotor defects as a result of expression of a mutant form of human TDP43 [4]. Drug efficacy was subsequently validated in zebra fish models based on the expression of mutant forms of human SOD1 and fused in sarcoma (FUS) [4]. The zebra fish models exhibit profound neuromuscular junction defects, and these were mitigated by pimozide treatment, prompting further investigation of neuromuscular synaptic function in mice that express the G37R variant of human SOD1 [4]. Ultimately, the putative mechanism of action for pimozide in these models was blockade of T-type Ca^{2+} channels at neuromuscular junctions to enhance neuromuscular synaptic activity [4]. Based on the positive outcomes in these model systems, a short-term trial in ALS patients was undertaken to assess safety and potential benefit. In very small numbers of patients, electrophysiological measures of muscle function suggested that the drug could be beneficial, and a long-term trial is currently underway (ClinicalTrials.gov Identifier, NCT03272503).

This example of bench to bedside drug development is a clear advancement in our clinical trial system. It offers tangible evidence to our desperately ill patients. The initial study of pimozide in patients, however, was only short term and did not include a treatment trial in a relevant animal model [4]. The study by Pozzi et al. in this issue of Neurotherapeutics sought to address whether long-term treatments with pimozide could improve motor function or extend life expectancy in two distinct mouse models [2]. Pimozide was administered at a dose scaled to mimic the human trial. While blood or CNS tissue levels were not obtained to confirm that the drug-reached target tissues at therapeutically relevant concentrations, available information on pimozide pharmacokinetics indicated that the dose used should be adequate. Interestingly, the authors found no significant benefit in neuromuscular function. In fact, life span in the treated G93A SOD1 mouse was shortened and muscle strength performance was not improved.

In this day of imminent "right to try" legislation, we have to be careful to provide desperate patients with access to potentially lifesaving drugs even when the evidence to support the use of such drugs may be inconclusive. The mouse models, while not perfect, reproduce certain aspects of the disease. These mice provide the opportunity to more closely study the disease course in a defined system and address the complex interactions of a biological system. Used in the appropriate context, the mice have the potential to be a

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key step in the "bench to bedside" development of new therapies. The genetic mouse models are clearly key intermediates in developing therapies that target a specific genetic defect, but whether, or which of, these genetic models are predictive pre-clinically for sporadic ALS remains uncertain. The initial studies of pimozide in short-term and narrowly focused human studies showed potential for benefit and its safety is well known, allowing it to proceed to longer term human trials. The newer preclinical study by Pozzi et al. suggests, however, that pimozide may not have the long-term benefits that patients are hoping for.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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