A newly approved drug for a rare group of diseases

Dichlorphenamide for periodic paralysis

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The periodic paralyses constitute a group of autosomal dominantly inherited myopathies characterized by acute and reversible attacks of muscle weakness associated with changes in serum potassium levels. In addition to paralytic episodes, patients may develop persistent and progressive muscle weakness. Over the past 2 decades, the periodic paralyses have been models for basic and translational research because they are the foundation for the development of the concept of channelopathies.[1–3] Before the discovery of disease-causing mutations in genes coding for the voltage-gated sodium, calcium, potassium, and chloride channels, disruption of such important proteins that have a central role in the genesis and propagation of action potentials seemed incompatible with life.[4,5] Investigators have subsequently found causal mutations in genes encoding ion channels in epilepsies, ataxias, and cardiac arrhythmias.[6] Periodic paralysis and related muscle ion channel disorders were also among the first diseases for which dissecting the action of a drug on its target directly influenced targeted treatment.[7] Finally, the periodic paralyses were among the first disorders in which understanding of the physiologic basis of symptoms enhanced diagnostic accuracy by electrodiagnostic testing and DNA sequencing.[8]

In this context, Griggs, Engel, and collaborators first used carbonic anhydrase inhibitors in periodic paralysis and advocated for developing treatments in periodic paralysis through international collaborations. Acetazolamide and dichlorphenamide are carbonic anhydrase inhibitors, which cause metabolic intracellular acidosis and increase calcium-activated potassium channel activity in models of periodic paralysis. These drugs have long been used off-label to diminish the number of periodic paralysis attacks. Because off-label drugs can, without notice, go off the market for regulatory or marketing reasons, the Griggs group worked to merge international efforts to study large patient cohorts with periodic paralysis to achieve adequate power to show proof of efficacy. The authors first performed 2 randomized, double-blind, placebo-controlled crossover trials with 42 patients with hypokalemic periodic paralysis and 31 patients with potassium-sensitive periodic paralysis. A washout period separated the two 8-week-long treatments. Dichlorphenamide reduced attacks or episodic weakness in both forms of periodic paralysis.[9] In the report in this issue, the authors describe the results of randomized, placebo-controlled, double-blind, and multicenter international phase III trials.

A 9-week placebo-controlled phase was followed by an extension phase with dichlorphenamide. Patients had precise diagnoses including a molecular diagnosis. Forty-four patients with hypokalemic periodic paralysis and 21 patients with hyperkalemic periodic paralysis were enrolled. The original design of the trial included an acetazolamide branch, but it had to be abandoned because of patient subjective preference for dichlorphenamide over acetazolamide due to perceptions about relative effectiveness and the adverse effect this had on recruitment. It is worth mentioning that this subjective patient perception added to the limits of the present study, preventing testing of a legitimate hypothesis. To increase accurate recording of events, patients were monitored with electronic diaries. The authors showed that dichlorphenamide was more effective than placebo, decreasing the number of hypokalemic periodic paralysis attacks, with an increased quality of life.[10] They also confirmed the safety of the drug; the most common adverse effects were paresthesiae and confusion. Limitations of the trial originate from insufficient recruitment; the target number of patients was not reached to enable conclusions regarding quality of life in patients with other forms of periodic paralysis. The authors comment on obstacles that prevent performance of international trials, mostly from the slow pace of local ethics committee approval and research and development processes, and the difficult adaptation of local regulations to the requests of international collaboration.

Despite its limitations, the work of Sansone et al. is good news for patients with rare diseases. It shows that academic research can have an important role in

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identifying the molecular causes for rare diseases, which facilitates development of new therapies to meet patient needs. It also shows that excellent patient-oriented clinical research can lead to rapid drug approval by the Food and Drug Administration.

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