EDITORIAL

Unintended Consequences of Approving Unproven Treatments—Hope, Hype, or Harm?

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In an aging population, the prevalence of neurodegenerative diseases is increasing. The impact is far reaching, creating social and economic burdens for an increasing number of families and producing significant challenges to a health care system that is straining to keep up. Patients, families, and physicians are desperate for effective treatments, and pharmaceutical companies are responding by spending billions of dollars on clinical trials of new drugs that are hoped will slow, stop, or even reverse the progression of disease. Also, given the enormous investment in science from the government, patient advocacy organizations, and individuals, there is disappointment that we have not done better in finding "cures" for these devastating diseases. There is also pressure, mostly from advocacy groups, for approval of new medicines that show even an inkling of potential benefit.

Related article

Edaravone is a free-radical scavenger originally developed in the 1980s and marketed in Japan for the treatment of acute ischemic stroke. It was repurposed for the treatment of amyotrophic lateral sclerosis (ALS) and is only the second disease-modifying drug approved for the treatment of ALS, the first since riluzole was approved in 1995. The approval of edaravone by the US Food and Drug Administration (FDA) in 2017 was somewhat of a surprise to many in the ALS scientific and clinical research communities but was seen by patients as new hope for slowing disease. The drug, tested only in Japan, had shown mixed results in 2 important clinical trials. The first phase 3 trial[1] performed in a large and diverse ALS population of 206 participants was deemed "negative" based on the analysis of response to the primary outcome measure—the ALS Functional Rating Scale-Revised (ALSFRS-R), a 12 question, 48-point patient-reported questionnaire that addresses various features of ALS disability. However, a post hoc analysis identified a subgroup of 67 study participants who appeared to respond positively in the trial. This subgroup met specific clinical criteria at baseline, including a higher functional status, shorter disease duration, and moderate rate of disease progression. In an innovative revised design with improved statistical power based on the deliberate selection of a more homogeneous ALS population, the sponsor performed another small phase 3 trial that included 137 study participants.[2] After 24 weeks, functional decline as measured by the ALSFRS-R was less in the edaravone-treated group. Although the difference between active and placebo treatments reached statistical significance, the actual mean difference was about 2.5 points, a value of uncertain clinical significance. The more quantitative measures of respiratory function and muscle strength showed no effect of edaravone. Those data raised concerns from some people in the research community about the true relevance of this finding for patients as a disease-modifying agent.[3,4] A subsequent analysis raised questions about the study design and also suggested that the modest benefits of edaravone may not outweigh the risks and complications of chronic intravenous administration, suggesting a net harmful effect of intravenous edaravone.[5,6]

In this issue of *JAMA Neurology*, Witzel and colleagues[7] in a collaboration among 12 German ALS referral centers, report a well-designed prospective observational study of edaravone, comparing patients who received edaravone to a control group of patients with ALS receiving standard care. In a particularly creative and important subanalysis, the authors identified a group of 64 treated patients who would have been eligible for the selective patient population of early onset, high-functioning participants enrolled in the "positive" Japanese trial. These potential trial participants were matched 1:1 to a group of concurrent patients undergoing standard treatment using propensity scoring matched for multiple baseline characteristics. Statistical comparisons of the primary outcome measure, change in ALSFRS-R slope, showed no differences between edaravone and standard treatment in all groups: the total 194 edaravone-treated patients, the selected subgroup, and also the group that did not meet the original targeted inclusion criteria. Similarly, there was no difference in survival probability among all the groups.

Although the results of an observational trial may be criticized as being less trustworthy than a prospective placebo-controlled trial, the rigor of this current virtual trial makes it both impressive and believable. The total number of edaravone-treated patients is 3 times the number included in the Japanese trial, and the number of subgroup patients and controls was equal to that in the original positive study. These new data certainly add to the conversation about the usefulness of edaravone for the treatment of patients with ALS. More so, these data add to the unfortunate experience in ALS clinical trials, in which exciting results in small trials are not reproducible in larger, appropriately powered trials.[8]

The approval of edaravone by the US FDA raises difficult questions about the quality and quantity of the data needed for registration and marketing of new ALS drugs. Certainly, the calculations leading to approval must be different for serious diseases with few or no available therapies, such as ALS and other neurodegenerative diseases. However, the marketing of drugs with little or no proven efficacy does not in any way improve patient care. The case of edaravone is particularly troubling. This drug, requiring continued intravenous injections and costing upwards of $150 000 per year, never underwent trial in the United States (which, if not unprecedented, is certainly unusual). There were conflicting results from the 2 trials

conducted in Japan, which would be expected to encourage a request from the FDA for a larger phase 3 trial before approval. Indeed, in the publicly available FDA Decision Memorandum on edaravone, it is stated that "the Office of Biostatistics is not enthusiastic with respect to approval,"[9(p7)] noting that the single positive study should be considered "hypothesis generating" only. Also, at the time of this writing, the European Medicines Agency has not approved edaravone and is requiring a larger and longer trial before consideration. Health Canada has approved edaravone, although use is restricted to patients who meet the same selective trial criteria.[10]

The desperate search for new ALS therapies and the desire to bring new drugs to market are understandable. Unfortunately, many patients and patient advocates blame the US FDA for the lack of new drugs, unfairly tagging the agency as an obstacle to effective therapies.[11] However, there are no examples of potentially game-changing ALS therapies that have not come to market owing to US FDA barriers. Our lack of effective therapies for ALS and other devastating neurodegenerative diseases reflects a lack of a clear understanding of underlying biological mechanisms and true druggable targets. Another case in point is illustrated by the controversy surrounding the recent US FDA approval to Biogen for the Alzheimer drug aducanumab. After conflicting results from 2 clinical trials, the FDA expert panel overwhelmingly voted not to approve but to require a third definitive trial. Nevertheless, aducanumab was approved, introducing to market an expensive medication that may provide more hope than true benefit.[12]

The marketing of drugs that do not generate data that show a consistent and incontrovertible clinical effect (and not just $P \leq .05$) may do more harm than good. Unproven drugs for neurodegenerative disease are frequently costly and burdensome for patients and may have toxic effects that outweigh any positive clinical effect. Also, there may be a negative effect on future clinical trials such that patients may choose not to participate based on their hope that this "new" drug is providing proven benefit. Resources may be diverted away from interventions that could actually be more tangibly helpful for patients, and patients may develop false hope based on unrealistic expectations. Furthermore, conflicting messages among clinician experts and regulatory agencies breed mistrust in science and the health care system. In these times of a global pandemic, it is clear that lack of trust in medicine and scientific processes has become a public health crisis.

All ALS and neurodegenerative disease stakeholders are hopeful that therapies that meaningfully improve the lives of patients will soon be discovered, and when this happens, any regulatory or bureaucratic barriers should be removed to bring the drug to market as soon as possible. Indeed, when the first successful gene therapy was discovered for spinal muscular atrophy, with striking benefits to study participants, the placebo group of the trial was removed, and the trial was terminated early to allow for accelerated approval. Scientific rigor and patient safety were preserved without withholding or delaying a game-changing therapy. Incremental progress is important in drug development and should be celebrated; however, accelerated approval of marginally helpful drugs does not bring us closer to the long-term goal of developing meaningful treatments to help patients with devastating diseases. The unintended consequences warrant caution for future drug approval decisions.

ARTICLE INFORMATION

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