Medical News & Perspectives

Questions of Safety and Fairness Raised as Right-to-Try Movement Gains Steam

Julie A. Jacob, MA

After Colorado enacted a right-to-try law in May 2014, Eva Feldman, MD, PhD, director of the program for neurology research and discovery at the University of Michigan, began receiving phone calls and emails from people in Colorado with amyotrophic lateral sclerosis (ALS). The state's new law allowed patients with terminal illnesses to petition drug manufacturers for investigational drugs and therapies without seeking Food and Drug Administration (FDA) expanded access (compassionate use) approval first. The ALS patients were inquiring if they could undergo the experimental stem cell therapy procedure for which Feldman and her team were conducting clinical trials (NCT01730716, NCT02058732) at the university.

In the end, however, all the patients decided against the procedure. Although Feldman and her colleagues were willing to teach the complex surgical technique to neurosurgeons in Colorado, it would cost patients up to $100 000, and the existing data aren't yet conclusive enough to know whether the stem cell therapy is effective.

"Each patient decided to wait for the next clinical trial or try less expensive, more easily available therapies," Feldman said.

The experience taught her that when it comes to the sensitive issue of permitting patients with terminal or degenerative illnesses to try investigational drugs and therapies through right-to-try laws, it is crucial to have a thorough discussion, and sometimes several, with patients about the potential benefits and risks, as well as the financial burden, of treatment.

"Patients with a lethal disorder are very desperate and will frequently be willing to try medications that you know as a physician may harm them," said Feldman.

Feldman's experience is one example of how individual freedom, revered in US society, underpins discussion and debate about whether patients with terminal illnesses should be able to try investigational drugs and therapies outside of clinical trials and the FDA expanded access program. Public interest has been heightened recently by the passage of right-to-try laws in 21 states since April 2014, as well as a push by people with ALS for accelerated FDA approval of GM604 (http://www.gm604.org), a drug developed by Genervon Biopharmaceuticals that has completed phase 2A clinical trial tests.

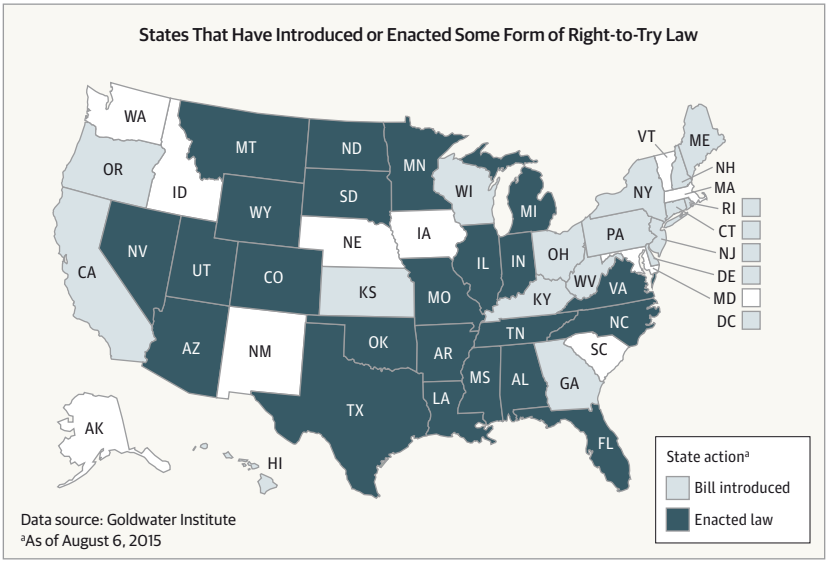
Right-to-Try

A patient's right to try an investigational drug is at the core of right-to-try laws (http://www.righttotry.org), which the libertarian Goldwater Institute has championed. Such laws allow patients with terminal illnesses, with their physician's consent, to request drugs that have undergone phase 1 clinical safety testing directly from pharmaceutical manufacturers, instead of applying through the FDA's expanded access program.

The Goldwater Institute became interested in the topic while researching the FDA's policy on emerging medical technologies. The institute heard stories about how time-consuming it was for physicians to complete the expanded access form, as well as the 2 to 4 months that it often took for such requests to be approved, explained Kurt Altman, the institute's director of national affairs and special counsel.

Yet bioethicists question whether such laws offer anything more than "the creation of false hope" (Caplan AL et al. *Expert Open Pharmacother*. 2015;16[9]:1275-1279). Individual patients with a serious or life-threatening illness can already request investigational drugs through the FDA's expanded access program. The FDA started the expanded access program in 1987, and in 2009, the FDA "clarified existing regulations and added a new expanded access category for intermediate-sized populations [more than 1 person but generally fewer patients than those treated as part of an investigational new drug application]," said FDA spokesperson Sarah Peddicord, who also said that such requests "proceed quickly."

Although the FDA declined to name specific investigational drugs for which individual patients have received expanded access approval, an FDA blog mentions drugs for cancer and rare pediatric diseases as categories of drugs appropriate for expanded access use (http://1.usa.gov/1J2wT52). The FDA receives about 1000 requests each year for expanded access, and 99% of the requests are granted (Blair Holbein ME et al. *Clin Transl*



Sci. doi:10.1111/cts.12255 [published online January 15, 2015]). It takes physicians about 2 hours to complete the expanded access form on behalf of an individual patient, according to Sandy Walsh, another FDA spokesperson, and the FDA is currently reviewing comments on a proposed streamlined expanded access application form (http://1.usa.gov/1f4ZKvq).

Although the right-to-try laws allow patients to bypass the FDA, patients must ask their physician to request the drug for them, Altman explained. The right-to-try laws are similar to the FDA's expanded access program in that both require a physician to make the request and permit the pharmaceutical company to decide whether or not to supply the drug.

The right-to-try laws may have been introduced and advocated as a result of the perception that the FDA drug approval process takes a very long time, commented pediatric oncologist Steven Joffe, MD, MPH, vice chair of medical ethics and health policy at the Perelman School of Medicine at the University of Pennsylvania.

"I think this is frankly incorrect, " said Joffe. "The data do not support that [the FDA is slow in approving drugs]."

The laws may also be an attempt to mitigate a 2007 decision by the US Court of Appeals for the District of Columbia that reversed the court's 2006 ruling that terminally ill patients have a constitutional right to experimental treatments, he said (Leonard EW. *J Law Med Ethics*. 2009;37[2]: 269-279).

Right-to-try laws are "symbolic of the desire for hope, that newer is always better," said Nancy Berlinger, PhD, a research scholar with the Hastings Center, a bioethics institute in Garrison, New York, noting that throughout the years, various drugs have been promoted as a promising option to treat a disease, only to be later proven ineffective.

Access Depends on the Manufacturer

Manufacturers may deny the right-to-try request, sometimes with good reason. The company may have a limited supply of the drug or could be concerned that if medication is made available without participating in a clinical trial, patients may not enroll in a trial to avoid the risk of being placed in the placebo group.

Manufacturers may also fear that an adverse reaction experienced outside of a clinical trial may jeopardize the chances of approval.

"It can cause a real problem with the development [of the drug] if you give it to someone who [is not an appropriate candidate] and something bad happens to that person," said Dave Wendler, PhD, head of the section on research ethics in the department of bioethics at the National Institutes of Health Clinical Center.

The Pharmaceutical Researchers and Manufacturers of America (PhRMA), while not taking a formal position on right-to-try laws, opposes allowing patients to bypass the FDA and clinical trial process. "Legislation at the state level, however well-intentioned, is unlikely to add any meaningful new approaches that can optimize the federal expanded access process overseen by the FDA," Sascha Haverfield, PhD, PhRMA's vice president of scientific and regulatory affairs, said in a written statement.

ALS Patients Advocate for Accelerated Approval

Dissatisfaction with the FDA approval process is driving a grassroots volunteer ALS organization, Hope Now for ALS, to petition the agency to speed up its approval of Genervon's drug, as well as any other potential drugs in development. In October 2014, Genervon, a small company in Pasadena, California, released the results of a phase 2A clinical study including 12 patients over 12 weeks that indicated a smaller decline in the forced vital capacity (FVC; the ability of a person to exhale air forcibly) among patients with ALS who took the drug.

In the study, 4 patients with ALS received a placebo and 8 patients received the drug GM604. The FVC decreased a mean of 22.61% in the placebo group, while in the treatment group it decreased 5.6% (http://bit.ly/1HikkQf). Since then, Hope Now for ALS has been lobbying the FDA to grant the drug accelerated approval status and began conversations with FDA officials in June. However, the organization stresses its lobbying campaign is broader than 1 drug.

"Our goal is to expedite the process, which will in turn bring more drug developers into the mix to develop their own treatments for ALS. By next year we would like to see multiple drug approvals, not just GM604," said Jehad Majed, a member of the grassroots organization. As of the time this issue of *JAMA* went to press, the company had not yet submitted a new drug application for GM604 nor had the study been published in a peer-reviewed journal.

In April, the FDA issued a statement calling for Genervon to "release all the data from their recently completed trial in order to allow a more informed discussion on the trial findings among ALS stakeholders" (http://1.usa.gov/1BzeMDJ). Genervon said that it has submitted all phase 2A data to the FDA but cannot publicly release all of its data because they are confidential and proprietary. The company also stated that it is waiting for the FDA "to

come up with a fast path moving forward for GM604 that satisfies all the parties involved." FDA spokesperson Walsh said that the FDA is "working closely with Genervon on the investigational drug GM604."

Overestimating Benefit, Minimizing Risk

Even when patients receive a drug through the FDA's expanded access program or through right-to-try laws, they may have unrealistic expectations and may not fully understand that the drug might cause adverse effects that may reduce the quality or length of life, noted ethicists.

Patients with terminal illnesses may argue they have nothing to lose, but an article in the *Hastings Center Report* discussing right-to-try laws noted that patients with terminal illnesses who try investigational drugs may end up having "shorter and more miserable lives" because of possible adverse effects (Dresser R. *Hastings Cent Rep*. 2015;45[3]:9-10).

For example, a person with ALS can live 3 to 5 years with current treatment therapies, but an experimental treatment that fails could cost them precious time, explained Feldman.

Physicians, too, are in a quandary, Wendler noted. They want to help their patients but know little about an investigational drug's efficacy and potential adverse effects, especially in the early stages of testing. Weighing a treatment's possible benefits against potential harm is difficult at best.

Questions of Fair Access and Transparency

According to ethicists, access to investigational drugs outside of clinical trials also raises the issue of fairness: who gets the investigational treatment and who doesn't? Those who do may be the most savvy about promoting their case, may have the best connections, and can afford to pay for an investigational drug outside of a clinical trial, rather than patients who are the sickest or the best candidates for the investigational treatment.

According to ethicists, access to investigational drugs outside of clinical trials also raises the issue of fairness: who gets the investigational treatment and who doesn't?

"There is a natural tendency to regard the needs and concerns of identifiable people more than the people you don't see pictures of," said Wendler.

What's more, if compassionate use compromises the ability of drug manufacturers to demonstrate that a drug is safe and effective, then the needs of the individual patient trump the need of society for assurance that the drug in question has been extensively tested, is safe, and works as intended.

"It interrupts the collection of data [and] competes with fairness to all patients who may potentially benefit from the drug," said Berlinger.

Yet if right-to-try laws are not the answer, then what is the best way to permit patients with terminal and degenerative illnesses to obtain investigational drugs while preserving the integrity of the clinical trial process?

Toward that end, Johnson & Johnson's Janssen Pharmaceuticals in conjunction with the New York University School of Medicine's division of medical ethics has convened a committee of medical experts, bioethicists, and patient representatives that is chaired by Arthur Caplan, PhD, the school's director of medical ethics.

Janssen will first review patients' requests and direct them, if appropriate, to clinical trials or the FDA's expanded access program. If neither program is appropriate, the company will then refer the request to the committee, explained Amrit Ray, MD, Janssen's chief medical officer.

Whatever method is used to decide, it needs to be fair and consistent, instead of decisions being made "on an ad hoc basis, when they pop up," said Wendler.

Transparency is important, too, the ethicists said. One bill addressing that issue is currently in the House Subcommittee on Health. The Andrea Sloan CURE Act, named after a Texas attorney who died from ovarian cancer, would require pharmaceutical companies developing breakthrough drugs to make their policies for compassionate use public (http://1.usa.gov/1HesaQh).

It's also important for physicians to consider how the approval process can be improved, noted Feldman.

"Right-to-try has opened up the eyes of practicing physicians and academics like myself," she said. "We need to look at the bigger picture and what we can do to facilitate and fast-track [drug approval] as we also go through the very rigorous and needed FDA process." ■