Unapproved drugs spark life-and-death debate

By Rita Rubin, USA TODAY

BALTIMORE — On a blustery January day, Rhett Davis relaxes in a recliner at Johns Hopkins Hospital as clear fluid drips from a hanging bag, through a tube and into a vein in his left arm. The 30-minute process is anticlimactic, considering what his family and his doctor went through to get the drug for him.

Davis, 32, was diagnosed with a rare blood disorder called paroxysmal nocturnal hemoglobinuria, or PNH, when he was 17, but his health didn't begin to deteriorate until about two years ago. The blood clots that kill nearly half of PNH patients destroyed his liver. His kidneys failed.

Since the week after Thanksgiving, though, Davis had been making six-hour round trips from his home in Kingston, Pa., to Baltimore for intravenous doses of eculizumab, the first drug shown to work against PNH. It wasn't approved by the Food and Drug Administration until March 16. Without the drug, Davis might have died by then, says his doctor, Robert Brodsky.

Every day, patients with life-threatening illnesses run out of FDA-approved treatments. In desperation, some seek drugs that have not yet been approved by the agency and, in some cases, have not even been widely tested. These patients argue they have nothing to lose and are willing to risk taking even a little-studied drug that offers a glimmer of hope.

But FDA officials, as well as many doctors, are concerned that even terminal patients are as likely to be harmed as helped by such drugs. And manufacturers and researchers worry that easy access to experimental drugs could stifle the development of new treatments by shrinking the pool of patients available for clinical trials.

Davis is typical of patients with life-threatening diseases who have been able to obtain experimental drugs outside of clinical trials. He didn't have time to wait for a new drug to arrive on the market, and he didn't meet the strict eligibility criteria for trials of drugs not yet approved.

Frustrated with the cumbersome process for obtaining experimental drugs — which requires dealing with the FDA bureaucracy as well as drugmakers and research institutions — a patient advocacy group has taken the FDA to court. The group argues that mentally competent terminally ill patients have a right to get such drugs.

Howard Fine, chief of the brain cancer branch at the National Cancer Institute, says he understands both sides of the debate over experimental drugs.

"Ethically speaking," Fine says, noting that he's talking only for himself, "who has the right to say to a patient: You have no right to try this medicine even though you're dying, even though you're well informed?"

On the other hand, he says, giving unapproved drugs to anyone who wants them would be a logistical nightmare: "Where are (drugmakers) going to send these drugs? The local doc down the street? And who's going to educate the doctor?"

Fine says he sees 2,000 to 3,000 brain tumor patients a year, the "vast majority" of whom will die within the next year. Sometimes they don't qualify for a clinical trial. Sometimes they can't deal with the hassle of it, especially if they live far from the National Institutes of Health's campus in Bethesda, Md. Fine says he gets calls from parents of dying children who plead: "Just give me this drug. What have we got to lose?"

A verdict in favor of the plaintiffs in the lawsuit against the FDA could eliminate patients' need to get the agency's permission to take experimental drugs. But many patients might still find roadblocks in cost, limited supplies and manufacturers' liability concerns.

On March 1, the U.S. Court of Appeals for the District of Columbia Circuit heard oral arguments in the case. Judge David Tatel got right to the point: "Who decides what's terminal, and how do you decide what lifesaving is? Suppose someone has a disease that will result in death in five or 10 years. Is that terminal?"

The court isn't likely to rule for several months, but the case already has divided doctors and patient-advocacy groups.

No 'slam-dunk' decision

"There are some good arguments on both sides," says Frank Palumbo, a lawyer and pharmacist who heads the University of Maryland School of Pharmacy Center on Drugs and Public Policy. "It's clearly not a slam-dunk for anybody."

The lawsuit over the FDA's barriers to the use of experimental drugs comes at a time when the agency also is under fire from critics who say it doesn't do enough to keep unsafe drugs off the market.

Opponents of easier access to experimental drugs argue that the drugs' early promise might not hold up. (For example, fewer than 10% of cancer drugs evaluated in Phase I trials, the first human tests, make it to market, the FDA says.) Instead of saving lives, some analysts say, drugs early in the developmental pipeline could end up shortening them.

"You don't want to put more weight than is appropriate into what a Phase I study shows," says bioethicist Arthur Caplan of the University of Pennsylvania. "Phase I studies are basically just trying to make sure you don't poison anybody by exposing them to stuff."

At best, dying patients might gain a few months of life from drugs that have undergone only Phase I testing, says Caplan, who supports making it simpler for patients to seek FDA permission to use experimental drugs.

"I'm not arguing that six months isn't good," Caplan says. But "just as it's good to live six more months, it's also good not to lose six months."

If the FDA loses the lawsuit, "companies could come along and sell false hope to patients," says Allen Lichter, CEO of the American Society of Clinical Oncology (ASCO), which submitted a "friend of the court" brief in February siding with the FDA.

The brief was co-signed by the American Academy of Medical Colleges and the National Coalition for Cancer Survivorship, which describes itself as the nation's "oldest survivor-led cancer advocacy organization."

"Yes, it's a little bit hard to get these drugs," Lichter says. "And to some extent, that's the way it should be. This shouldn't be as easy as walking down to the drugstore and buying a package of Tylenol."

Providing experimental drugs to all comers could hamper clinical trials, says Alan Goldhammer of the Pharmaceutical Research and Manufacturers of America (PhRMA), the prescription drug industry's main trade group.

"Companies must be careful to make sure that after making experimental drugs available to more patients, they are able to find enough volunteer patients willing to abide by the restrictions and rules of a clinical trial," Goldhammer said in a statement.

But proponents of easier access to experimental drugs say patients are dying because they don't meet clinical trials' strict criteria.

Abigail's story

Abigail Burroughs was one of them, says her father, Frank Burroughs. Abigail had tumor cells that contained an enzyme called the epidermal growth factor receptor, or EGFR, which acts as an "on" switch, triggering cells to divide and spread without dying.

At the time, Erbitux and Iressa were being tested against tumors with EGFR in the colon and lung, respectively. But her tumor was in the head and neck, so she was ineligible.

Both drugs eventually won FDA approval.

After Abigail died in June 2001 at age 21, Frank Burroughs co-founded the Abigail Alliance for Better Access to Developmental Drugs. The Fredericksburg, Va.-based organization and the non-profit Washington Legal Foundation brought the lawsuit against the FDA that seeks increased access to experimental drugs.

"The point we make in our lawsuit is really an important one: The decision should be made by the patient in consultation with their doctor," Burroughs says. "We feel the FDA should not be overly paternalistic."

Emil Freireich, director of adult leukemia research at the University of Texas M.D. Anderson Cancer Center, agrees. When Freireich heard that ASCO, which he co-founded, had filed its court brief supporting the FDA's limits on experimental drugs, "I almost cried," he says.

"It's a really sad, sad day when an organization that represents all the oncology physicians in the world sides with the FDA over the interest of patients," Freireich says.

"I asked five leading (scientific) investigators to side with Abigail," Freireich says. "They all demurred, because they're scared the FDA is going to kick them in the butt."

'Compassionate use'

Rhett Davis obtained eculizumab through a treatment "IND" — short for investigational new drug — which is like a clinical trial for a single patient.

Just before it approves drugs, the FDA sometimes makes them available to groups of patients. The two-decade-old practice, known as "compassionate use," resulted from pressure by AIDS activists who demanded access to experimental drugs to treat what was then an imminent death sentence.

Brodsky, Davis' doctor and chief of hematology at Johns Hopkins, co-wrote a *New England Journal of Medicine* report in September on a Phase III trial that found eculizumab reduced the destruction of red blood cells in PNH patients and their need for transfusions.

Only those who were dependent on blood transfusions could enroll in the trial. When it was open for enrollment, Davis didn't qualify because he wasn't dependent on transfusions. By the time he required transfusions and became eligible for the trial, it was full.

As Davis lay in a hospital in Wilkes-Barre, Pa., last November — his skin tinged yellow because of his failing liver, fluid accumulating in his abdomen because of his failed kidneys — his family pressed their senator and congressman to help them obtain eculizumab.

Meanwhile, Brodsky applied to Alexion, the drug's maker, the FDA and the Johns Hopkins institutional review board, which must approve all human research at the hospital, so Davis could get the drug.

Davis could be considered for a lifesaving liver transplant only if he received the drug and it worked, Brodsky says. The day before Thanksgiving, Davis learned he would get his eculizumab.

Even if the Abigail Alliance wins its lawsuit against the FDA, the case might have a minimal effect on patients, Palumbo says. "It might be that (only) people with money and access to other professionals might be the real winners."

The lawsuit asks that terminally ill patients be allowed to pay for promising drugs that are not yet on the market. In December, the FDA proposed revisions to rules about how drugmakers can charge for experimental drugs. The ability to recoup costs might spur smaller companies to provide more drugs outside trials, FDA Deputy Commissioner Janet Woodcock says.

Still, no matter the verdict, even patients who could pay for experimental drugs might find makers unwilling to provide such drugs.

"Often, we are given as the reason" why patients can't get an investigational drug, Woodcock says. "But, if really questioned, the companies will say, 'We're not giving it out.' "

PhRMA's Goldhammer notes that companies often make just enough of such drugs to use in clinical trials.

Liability concerns loom large, because the FDA prohibits patients who get an experimental drug outside a clinical trial from waiving their right to sue the drugmaker if they have adverse effects, Baltimore lawyer Mark Gately says.

Gately spoke last month in Washington at a forum on the Abigail Alliance lawsuit. "The very risk of being sued," he says, "is a major disincentive to providing drugs in this situation."

A success story

Davis could be considered an example of what can go right when a desperately ill patient gets a drug before it goes on the market.

The call came Feb. 6, more than two months after Davis began taking eculizumab and began to show improvement.

By that night, Davis was having liver transplant surgery at Johns Hopkins. He left the hospital nine days later. Now, he's planning to return to work as an auditor by summer.

"He is perfect," Brodsky says. "His PNH, you wouldn't even know he has it anymore. His kidneys are fine. His liver is fine. No more fluid on him. He's not that horrible color he was.

"It was really the drug that made this possible."