Using this information, we determined that the time it takes to bring innovative, high-risk devices to patients in the United States is similar to or shorter than that in the top four European markets (see figure). The public (CMS) process in the United States takes approximately as long as those in Italy and Britain, approximately half as long as that in France, and less than a third as long as that in Germany. The difference in time to market access is even greater when it comes to private insurers (covering the majority of the U.S. population), which often make reimbursement decisions within a few months after FDA approval.

To further illustrate this point, we compared the time to approval for five innovative, high-risk medical devices available in France, Italy, and the United States (see table). These case studies indicate that the average time to market access for these devices was 26.3 months in France, 30.8 months in Italy, and 15.3 months in the United States.

These numbers may not fully capture the reasons why a device reaches the market more quickly in one country than in another and do not reflect experiences with all innovative, high-risk devices. However, unless one uses equivalent standards in terms of the level of risk, the start and end points of the process, and the key end point of market access, accurate comparisons cannot be made.

The time it takes to bring innovative, high-risk devices to patients in the United States is similar to or shorter than that in the top four European markets.

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From the Office of Planning, Office of the Commissioner, Food and Drug Administration, White Oak, MD.

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The Ethics of Early Evidence — Preparing for a Possible Breakthrough in Alzheimer's Disease

Justin Lowenthal, B.S., Sara Chandros Hull, Ph.D., and Steven D. Pearson, M.D.

Related article, p. 570

Being on the cusp of a potential medical breakthrough for a serious disease can pose substantial ethical challenges. One current example arises from a recent study demonstrating — in a single mouse model in one laboratory — that the drug bexarotene is effective in treating Alzheimer's disease (see article by LaFerla in this issue of the *Journal*, pages 570–572). Administration of bexarotene resulted in a greater-than-50% reduction of β-amyloid plaque at 72 hours and substantial reversal of neural, cognitive, social, and olfactory deficits, albeit with reduced effects as the mice aged.[1] A single report of this kind of preliminary evidence will require confirmation before Alzheimer's disease investigators even consider launching clinical trials in humans. But unlike many drugs under study for Alzheimer's disease, bexarotene is not a novel experimental drug; it is already approved by the Food and Drug Administration (FDA) for treatment of a cutaneous form of non-Hodgkin's lymphoma. Therefore, physicians could currently legally prescribe it for off-label indications.

Although the results in the mouse model are too preliminary to generate more than the most cautious optimism among researchers, they are already creat-

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ing an important ethical dilemma in physicians' offices nationwide.[2] If patients with progressive Alzheimer's disease and their families, having read about this study online, begin asking their primary care physicians to prescribe bexarotene, what should physicians do? Writing an off-label prescription is completely permissible and would fulfill family members' desire to try anything to help their loved ones. But is it the right thing to do? And what if bexarotene is tested in a handful of patients, the results look promising, and the same scenario plays out in thousands of exam rooms? What issues relevant to individual patients and society must be considered?

One might argue that especially for a terminal, untreatable disease, one relevant ethical value is the autonomy of patients and their caregivers to seek access to promising treatments, in consultation with the physicians they trust. But because bexarotene has been approved by the FDA for the treatment of refractory cutaneous T-cell lymphoma (CTCL), we already have data on potential risks, at least in patients with CTCL. Bexarotene is known to induce lipid abnormalities in many patients, including high fasting triglyceride levels and hypercholesterolemia, and it can affect the action of insulin in patients with diabetes.[3] It has also been associated with increased risks of acute pancreatitis, elevated liver-function values, hypothyroidism, and leukopenia.[3]

Given these known risks, without evidence that bexarotene will be effective against human Alzheimer's disease, and absent any guidance as to the appropriate doses for this condition, the proper exercise of clinical judgment should certainly lead physicians to counsel patients and families that it is premature to prescribe bexarotene for this purpose. Even if patients and families are willing to take the risks for the potential benefit, the physician's answer should be no. This stance is consistent with longstanding ethical and professional guidelines.[4]

But what about the hypothetical future scenario in which early testing of bexarotene in humans has yielded "promising" results? The medical community would face an unusual situation: there would be sudden overwhelming demand for an approved drug to be prescribed off-label. Under these circumstances, the risk–benefit calculus might appear to shift for both patients and physicians. Physicians might start to feel justified in prescribing it for specific patients. Drugs are commonly used off-label when there are no approved options or when patients have had limited benefit from existing options. One example is the use of modafinil for chronic fatigue syndrome, multiple sclerosis, and Parkinson's disease.[5] But the prevalence of Alzheimer's disease would probably cause unusually intense demand for off-label prescribing of a "promising" drug.

Under these circumstances, additional important ethical issues must be considered — not only by individual physicians, but also by patient advocates, policymakers, and other stakeholders. Among these considerations are continued uncertainty regarding the balance of risks and benefits for individual patients, the importance of gathering reliable evidence through clinical trials to inform the care of future patients, the fairness of present and future access, and the value of stewardship of limited resources.

Although the off-label status of bexarotene creates a distinctive situation, we may benefit from examining the history of the advent of promising new drugs for human immunodeficiency virus (HIV) infection. In 1990, early results from human studies of several new HIV drugs created intense patient demand for broad access. The FDA mechanisms governing experimental treatments allowed access only for patients enrolled in narrowly defined clinical trials, with exceptions limited to those meeting restrictive eligibility criteria. The clinical research community needed to balance respect for patients' desire to try a promising therapy for a fatal disease against the need to run clinical trials, some of them placebo-controlled, in order to

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develop reliable evidence on the safety and true relative effectiveness of the new drugs. It was also viewed as critical that vulnerable and disadvantaged patients have equal access to the drugs and that the financial burden on patients, health insurers, employers, and the entire health care system be considered.

Ultimately, the FDA adopted a new, more flexible "parallel track" approach that allowed open-label therapeutic protocols to be run in parallel with standard clinical trials. Although this approach could not perfectly address all the different ethical goals, it represented an important attempt to engage all the stakeholders — including patients with HIV, whose voices were powerful and critical — in creating new models for early access without crippling the effort to develop better evidence. These models became key precursors to current regulatory mechanisms that specify the conditions under which patients can gain "expanded access" to drugs before regulatory approval.

Bexarotene's case is different, since off-label prescribing is already possible, but many of the ethical issues are similar and call for analogous deliberative procedures. We believe that all relevant stakeholders — patients, advocacy organizations, physician societies, investigators, the manufacturer, insurers, and FDA policymakers — should convene to produce guidance on how to address the potential demand for bexarotene. Recommendations for the situation today should be clear and unequivocal: bexarotene should not be prescribed before any human tests have been completed. Physicians should welcome the support of a broad stakeholder group in laying out the guidance's rationale and justification, which can be shared with patients and families.

But equally important would be this group's laying of the groundwork for future deliberation and guidance. All the ethical values and logistic trade-offs would have to be delineated to guide decision making as evidence evolves, and a transparent process would be needed for weighing these values and producing guidance, including standardized eligibility criteria for off-label prescribing of bexarotene. Physician societies should not try to address this challenge alone; it would be crucial, as it was with HIV, to engage with a broad spectrum of patient advocates and others to produce guidance with true legitimacy. Such a discussion could provide a model for future situations with other therapies.

In the spirit of the parallel track developed for HIV trials, creative mechanisms for clinical trials and registries should be sought to balance the goals of access, affordability, and evidence development. For example, depending on the results of early human testing, it might be possible to strike the right balance through the use of comprehensive registries and associated requirements linking insurance coverage with participation in evidence development.

The early promise of bexarotene in a mouse model of Alzheimer's disease is exciting. It is still extremely premature to believe that an effective treatment for Alzheimer's disease in humans has been found, but it is not premature to plan for such a possibility. Physicians, patients, and families are already confronting hints of the ethical challenges that may lie ahead; the time to discuss them formally is now.

The views expressed in this article are those of the authors and do not necessarily reflect the official opinions or policies of the National Institutes of Health or the Department of Health and Human Services.

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From the Department of Bioethics, Clinical Center (J.L., S.C.H., S.D.P.), and the Office of the Clinical Director, National Human Genome Research Institute (S.C.H.), National Institutes of Health, Bethesda, MD; and the Institute for Clinical and Economic Review, Massachusetts General Hospital Institute for Technology Assessment, Boston (S.D.P.).

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