COMMENTARIES

Incentivizing Drug Development for Patients With Rare Diseases

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Introduction

Prior to entering medical school, I worked as an overseas missionary and researcher working alongside patients with rare diseases or disorders. The patients I worked with had Hansen's disease (previously known as leprosy), a condition caused by a bacterial infection that is extraordinarily rare in most parts of the world. The infection, left untreated, can eventually lead to disfigurement, blindness, the inability to feel with one's fingers, paralysis of fingers and toes, and a tremendous amount of stigma.

I remember one patient named Ernesto. Years of delayed diagnosis and lack of access to trained health care professionals led to years of isolation away from society. By the time Ernesto showed up at our hospital—or more accurately, was left there by his family—the damage to his body and spirit was done: his fingers had curled and become unusable, he could not feel or communicate through touch, he was nearly blind, and he was abandoned by those closest to him. There was not much I could do except ensure that he was treated with dignity from that point onwards. I would come to understand that his story is a common one experienced by people with Hansen's disease. They often feel that they have been forgotten by society and the health care systems that are supposed to care for them.

Over time, I came to empathize with the patients. While working with these patients, I would often wonder whether anyone in the general public cared about these human beings or about the small but passionate group of individuals taking care of them. In 2019 alone, the National Institutes of Health provided $39 Billion for research, of which 0.1% was allocated for rare diseases.[1] But statistics can only capture so much about the problem. On occasion, I would visit academic health care conferences stateside and represent these patients. I remember the look on people's faces; I was clearly a zebra in their world of horses. For a long time, I felt isolated, as if those patients and I were on an island. I eventually realized that in our world where so much attention and resources are focused on big ticket issues such as cancer, diabetes, and hypertension, someone had to stand up for those without a voice. That realization catapulted me to medical school, where I am now.

I am a leader in our school's rare disease interest group and a participant in the RARE Compassion Program, where medical students have individual conversations with patients with rare diseases throughout their training.

Teaching to the Horses

Medical school teaches us long lists of drugs for common clinical conditions such as cancer, diabetes, and hypertension. For big-ticket conditions, we often have many options for classes of treatment. For hypertension, there are diuretics, angiotensin-converting enzyme inhibitors, and calcium channel blockers. Additionally, there are often multiple brand or generic options within those classes, as well as backups if those classes do not help.

From my perspective, perhaps one of the most compassionate things we can do for patients with rare diseases or disorders is to give them a chance at effective therapy, just as we strive to do for patients with cancer, diabetes, and hypertension. Luckily for patients with Hansen's disease, there is a curative treatment regimen. But for at least 95% of rare diseases or disorders, having even a single effective therapy would be a godsend. Less than 5% of rare diseases are manageable with approved therapies.[2]

Individuals living with rare diseases are not as rare as you might think. At least 1 in every 10 US residents has a rare disease.[3] More than likely, someone in your life could have a rare disease that does not have an effective therapy, much less a cure.

Federal Response and Market Incentives

In response to the lack of drug development for small patient populations, the federal government passed the Orphan Drug Act (ODA) in 1983. The goal of the ODA was to incentivize drug development for diseases or conditions impacting fewer than 200 000 individuals in the US. In exchange, the first sponsor of an orphan drug that became approved by the Food and Drug Administration (FDA) for a designated rare disease or condition would receive market exclusivity for 7 years. This is in comparison with the standard 5 years for a new chemical entity for a common illness. Additionally, the original bill allowed sponsors to claim a tax credit of up to 50% for qualified clinical testing expenses. Note that this is different from the research and development tax credit, which tends to be more limited in utility for orphan drug development and the specifics of which are beyond the scope of this article. Both can be collected for different development stages.

The impact of the ODA is tangible. Before the ODA, only 38 drugs were approved by the FDA to treat rare diseases. Since the passage of the ODA, more than 1100 orphan drug designations have been approved.[4] An orphan drug designation does not always lead to marketing approval, but it has given hope and some tangible benefit to patients with 1 of more than 7000 rare diseases.

Understandably, whenever lawmakers want to tinker with the ODA, patients with rare diseases fear losing access to innovative drugs in research and development that may help improve their conditions. In 2017, Congress cut by half the tax credit given to manufacturers of orphan drugs for clinical testing expenses related to drug development.[5] Congress cut this incentive at a time when orphan drug designations were at the highest they had ever been, fearing that pharmaceutical companies were taking advantage of the ODA. Since then, the number of orphan drug designations per year has not increased and has reached a plateau.[6]

This is a misguided action that must be reversed. With only 16% of therapies receiving orphan designation going on to earn FDA marketing approval, engagement in the ODA must be encouraged, not discouraged.[6] The fact is that developing drugs for rare diseases or disorders is challenging. According to the EveryLife Foundation for Rare Diseases, "a treatment for 10 patients in the US is held to the same standard as a treatment for 10 million patients."[7] When you combine lower ODA incentives with the FDA's strict expectations for rare disease drugs, the inherently high risk of failure in any drug development process, and add on the fact that many of these rare diseases affect much smaller populations, then you begin to understand how pharmaceutical companies may question whether it is worthwhile to develop drugs for rare diseases or disorders.

Lowering incentives and hoping that drug companies will continue to make products for rare conditions is setting physicians and patients up for failure. Public anger against drug prices for compounds to treat diabetes may be reasonable, but focusing on rare diseases as a scapegoat is unfair to the patients who have no fallback option.

Other options for encouraging orphan drug development include amending the ODA to provide additional guidance to the FDA on defining and applying regulatory flexibility for orphan drugs. At present, there are no guidelines for how the FDA should apply flexibility to rare disease drugs not meeting the traditional requirement of 2 adequate and well-controlled trials.[6] For example, randomized clinical trials are notoriously difficult to conduct for rare diseases or disorders. In a review of challenges of clinical trials in rare diseases, several were noted, including low patient numbers necessitating multicenter phase 1 and 2 trials; difficulties selecting a meaningful or relevant endpoint due to a lack of understanding about the natural history of rare diseases; and ethics of double-blind placebo-controlled trials when there are limited research participants.[8] The FDA already has several years of experience applying flexibility to approve rare disease treatments. A comprehensive review of that precedent experience ought to yield useful insights that could translate successfully into guidance for the FDA.

Continued Threats to Rare Disease Drug Development

A potential threat on the horizon for orphan drug development is implicated in the Inflation Reduction Act of 2022. If implemented as written, orphan drugs with a single orphan indication would avoid price negotiation. However, orphan drugs may carry multiple orphan indications and may be subject to price negotiation by the Centers for Medicare & Medicaid Services (CMS) soon after the launch of additional indications beyond the first indication. For example, if an orphan drug enters the market with one orphan indication and is later approved for an additional orphan indication, that drug may be placed under negotiation. The statute does not specify what CMS should do in these instances. It is unclear how CMS would interpret the statute to handle these situations and how those decisions may impact orphan drug development.

The political tension in the US today over drug affordability stems from serious concerns about equity and access. However, we must remember patients with rare diseases or disorders, especially when making policy decisions that impact the balance of market forces. The availability of therapeutics for rare diseases may prove to be very sensitive to market and regulatory incentives. To deny incentives for pharma risk-taking in rare disease is to tell patients like Ernesto that they should be happy with their lot while the majority of other patients are able to access multiple drugs for their more-common conditions.

Disclaimers and Conflict of Interest Statement

There are no financial disclosures or conflicts of interest reported.

Additional Information

Patient names were altered for privacy.

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