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COMMENTARY

The implications of Industry-Funded Disease Awareness Campaigns in the Rare Disease Setting

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In 1983, the US Congress enacted the Orphan Drug Act to incentivize pharmaceutical companies to develop drugs, vaccines, and diagnostic agents for rare diseases.[1] The Act offers 7 years of marketing exclusivity, a 25% tax credit (50% before 2017) on qualified research and development costs, and research subsidies for *orphan diseases*, defined as conditions that affect less than 200,000 people in the United States. Since its passage, the number of orphan drugs has risen dramatically. In 2018, 58% of all new drug approvals had a rare disease indication.[1]

One overlooked issue is that approval of an orphan drug may alter the frequency of the disease. Practitioners may be more vigilant to test for, screen for, or diagnose a condition with an approved therapeutic option. In many cases, increased diagnostic enthusiasm may be fueled by corporate sponsors through educational programs, conference sponsorships, and direct outreach to patients. If diseases are diagnosed more frequently after approval, then pivotal trial data may misestimate therapeutic efficacy. This situation occurs for the simple reason that all trial data apply to populations only as they were identified and enrolled in the study. If novel diagnostic criteria or increased vigilance is later applied, it is possible that population characteristics shift, disease severity lessens, and the efficacy of the therapy is altered. In this article, we discuss the implications of 3 rare disease awareness campaigns supported by pharmaceutical companies and consider potential corrective steps.

TRANSTHYRETIN AMYLOID CARDIOMYOPATHY

Consider the case of transthyretin amyloidosis (ATTR) cardiomyopathy (CM), a rare condition in which amyloid deposits build up in the heart, increasing wall thickness and impairing function, often leading to heart failure and arrhythmias.[2] In May 2019, tafamidis was approved for ATTR-CM, the first drug to receive approval by the US Food and Drug Administration (FDA) for the condition.[3] The approval was based on a randomized trial in which patients' diagnoses of ATTR were confirmed by biopsy of cardiac and noncardiac sites and their CM diagnoses by echocardiography that revealed intraventricular wall thickness exceeding 12 mm, a history of heart failure, and at least one prior hospitalization due to heart failure.[2] These specific inclusion criteria are critical in defining a cohort of patients in whom a common diagnosis—CM—is far more likely to be due to amyloid deposits.

Three months after the drug's approval, experts in the field advocated for screening through a publication titled "Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice."[3] The authors determined that ATTR-CM was underdiagnosed and that early treatment was essential for appropriate patient care, based on discussions at an expert scientific meeting funded by Pfizer Inc.

However, prior to the push to expand diagnostic testing, ATTR-CM was preferentially diagnosed in patients with unexplained CM. In the pivotal trial leading to approval, patients were excluded if their heart failure was thought to be driven by another process.[2] Moreover, many older patients with CM may have incidental amyloidosis, but cardiac dysfunction may be sequelae of multifactorial processes. As such, screening for ATTR-CM has the potential to make a rare disease more common and change the

characteristics of patients who receive the treatment. This result may improve outcomes—identify more eligible patients who benefit—or worsen outcomes—lead to the treatment of individuals whose CM is multifactorial, who do not derive commensurate gain.

SPINAL MUSCULAR ATROPHY

A second case concerns spinal muscular atrophy (SMA), a rare genetic neuromuscular disease that causes muscle wasting in both infants and adults. The severity of the disease differs depending on SMA type. Spinal muscular atrophy type 0 (SMA0) is the most severe, while SMA3 and SMA4 are less severe, having no effect on life expectancy.[4] In 2016, the FDA approved nusinersen, the first drug indicated for the treatment of children and adults with all SMA types.[4] The approval was based on interim results from the ENDEAR (Efficacy and Safety of Nusinersen in Infants With Spinal Muscular Atrophy) trial, a randomized controlled trial that found that among infants with SMA1, those treated with nusinersen were significantly more likely to have a *motor milestone response* (defined as improvement in at least one category of the Hammersmith Infant Neurological Examination and more categories with improvements than categories with worsening) compared with those in the control group.[5] Although the trial only investigated nusinersen's effect on patients with SMA1, the FDA approved the drug for all SMA types.

Currently, 20 states have adopted and implemented newborn SMA screening programs, and more have developed pilot programs with intent to implement. Cure SMA, a nonprofit group, has been advocating and lobbying for newborn screening since the approval of nusinersen in 2016. The organization has close ties to Biogen, the manufacturer of nusinersen. By screening for SMA, it is likely that the population of patients given the disease label and treated with nusinersen is different than those included in pivotal trials. After all, what parent would choose to omit therapy for their child when told they are suffering from a progressive neurologic ailment?

POLYCYTHEMIA VERA

In December 2014, the FDA approved ruxolitinib for patients with polycythemia vera (PV) and an enlarged spleen whose red blood cell counts insufficiently respond to standard treatment.[6] Polycythemia vera is a rare hematologic malignancy with an annual incidence of 1 in 36,000 to 100,000 persons.[6] According to the World Health Organization, a diagnosis of PV requires 3 major criteria—elevated hemoglobin level, a bone marrow biopsy specimen showing hypercellularity, and the presence of a *JAK2* mutation—or 2 of these major criteria and 1 minor criterion, eg, low erythropoietin levels.[7] However, these criteria are not highly sensitive or specific to PV and can present because of other health issues. Hemoglobin levels may fluctuate, and there may be a population of healthy people with *JAK2* mutations, now recognized as clonal hematopoiesis.

In 2017, Incyte Corporation teamed up with the daytime TV drama "General Hospital" to create an episode to bring PV awareness to the general public.[8] In this case, the awareness campaign may have encouraged patients and health care professionals to consider PV. Given the disease's flexible diagnostic criteria, it is possible that some patients diagnosed as having the condition may have been unrecognizable previously.

POTENTIAL ISSUES AMONG RARE DISEASE AWARENESS CAMPAIGNS

When disease campaigns change the scope of patient populations, the impact could be positive or negative. Provision of a disease-modifying agent to more people who may benefit could improve health outcomes in the population. However, patients who deviate from trial populations could derive less or no therapeutic benefit. For instance, older patients with multifactorial CM and incidental amyloid deposits may not benefit from tafamidis, nor may patients with asymptomatic SMA, who would be subject to intrathecal infusions and its attendant risks. This situation is particularly true for rare disease treatment in which the pivotal trials are more likely to measure surrogate outcomes rather than clinical outcomes and

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be more likely to have more cases of serious adverse events.[9] Moreover, health care professionals may be blind to therapeutic inefficacy, eg, a patient with SMA who advances through motor milestones would be declared a success of therapy even though improvement may have occurred in the absence of therapy.

The costs of these treatments also cannot be ignored. Ruxolitinib can cost between $91,000 and $143,000 annually. At a price of $225,000 per year, tafamidis is currently the most expensive cardiovascular drug in the United States,[10] while nusinersen is priced at $750,000 for the first year of treatment and $375,000 each year thereafter and is prescribed as a lifetime treatment.[10] The high costs of these drugs will not only limit access and add a financial burden to the US health care system but may also create a barrier for comparative efficacy trials on more affordable treatments.[11]

To address these challenges, we suggest that the FDA take 2 actions. First, the agency should impose risk evaluation and mitigation strategy programs on rare disease treatments requiring physicians and patients to attest to the indication for which the drugs were approved. Second, the incidence of orphan diseases before and after FDA approval should be monitored. If sizable deviations are observed, the FDA should be given the regulatory authority to demand confirmatory studies in the new population. Tafamidis may be a lifesaving drug based on a diagnosis made in 2014, but what is its effect in 2021 if the diagnosis is made more frequently or loosely? Disease awareness in orphan diseases makes us revisit the longstanding question in medicine: Does efficacy translate into effectiveness in a shifting medical landscape?

CONCLUSION

The current incentivization for rare drug development may have unintended consequences. Industry-funded campaigns to promote disease awareness may contribute to broader diagnoses and inappropriate treatment. By creating a risk evaluation and mitigation strategy program for rare disease treatments and monitoring the incidence of orphan diseases before and after regulatory approvals, the FDA can better regulate the orphan drug market and ensure that patients are receiving appropriate, effective treatments.

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REFERENCES

1. Sarpatwari A, Beall RF, Abdurrob A, He M, Kesselheim AS. Evaluating the impact of the Orphan Drug Act's seven-year market exclusivity period. *Health Aff (Millwood)*. 2018;37(5):732-737.
2. Maurer MS, Schwartz JH, Gundapaneni B, et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018; 379(11):1007-1016.
3. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail*. 2019;7(8):709-716.
4. Bodamer OA. Spinal muscular atrophy. In: Dashe J, ed. *UpToDate*. Waltham, MA: UpToDate; 2020. www.uptodate.com. Accessed June 1, 2020.
5. Finkel RS, Mercuri E, Darras BT, et al; ENDEAR Study Group. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017;377(18):1723-1732.
6. FDA approves Jakafi (ruxolitinib) for the treatment of patients with uncontrolled polycythemia vera [press release]. Incyte Corporation; December 4. 2014: https://investor.incyte.com/press-releases/press-releases/2014/FDA-Approves-Jakafi-ruxolitinib-for-the-Treatment-of-Patients-with-Uncontrolled-Polycythemia-Vera/default.aspx. Accessed June 1, 2020.
7. World Health Organization (WHO) diagnostic criteria for primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET). Incyte Corporation; 2016. https://www.mpnconnect.com/pdf/who-diagnostic-criteria-mf-pv-et.pdf. Accessed June 1, 2020.
8. Mailankody S, Prasad V. Pharmaceutical marketing for rare diseases: regulating drug company promotion in an era

of unprecedented advertisement. *JAMA*. 2017;317(24):2479-2480.

9. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA*. 2011;305(22):2320-2326.

10. Confidio. 3rd Quarter 2019 Pipeline Report. https://confidio.com/wp-content/uploads/2019/06/CON-Q3-2019-Pipeline-Report.pdf. Accessed June 1, 2020.

11. Gurwitz JH, Maurer MS. Tafamidis—a pricey therapy for a not-so-rare condition. *JAMA Cardiol*. 2020;5(3):247-248.