Specialty Healthcare Benefits Council
Defining Specialty Health

The Impact of Rare Diseases and Drug Therapy

David A. Kvancz, MS, RPh, FASHP

ABSTRACT

There are more than 7000 known rare diseases that affect a worldwide patient population that, if aggregated together, would be the third most populous country in the world. However, timely and accurate diagnosis, the use of effective treatment and maintenance therapies, and known prognoses for these patient populations are often challenging due to a number of factors. These challenges include access to, and validation of, clinical knowledge for a timely and effective diagnosis, treatment and maintenance therapies, and long-term prognosis due to very limited patient populations and individual provider expertise within each disease state.

Am J Pharm Benefits. 2016;8(4):000-00

Since the passage of the Orphan Drug Act in 1983, there has been significant acceleration in the number of pharmaceutical compounds identified, developed, and approved for the treatment of rare diseases, particularly within the past decade. The development and implementation of a rare disease strategy and management program by healthcare provider organizations and payers could greatly assist in improving the clinical, psychosocial, and economic impacts for this patient population.

Today's pharmaceutical market is increasingly driven, both from a marketing and a financial perspective, by drug products with narrow therapeutic indications and/or patient populations. This is in direct contrast to the last several decades in which the development of medications for acute or chronic disease states, affecting millions of patients, was the primary target for the pharmaceutical industry. Also contributing to this market shift are the development of "lifestyle" drugs and other medications for newly discovered and sometimes vaguely defined disorders or disease syndromes that, heretofore, may have been traditionally considered part of the human living experience and aging process. But, within the past decade, the accelerated application and approval of drugs designated for orphan status to treat rare diseases in very limited numbers of patient have become increasing concerns for all stakeholders in the healthcare marketplace. These disease states and drugs often have significant health, psychosocial, and economic impacts. The purpose of this paper is to provide an overview of this information as a baseline for understanding this rapidly growing field within drug development and utilization.

Definition and Statistics

As there is no agreed-upon, worldwide threshold prevalence or incidence for what constitutes a rare disease, the definition often varies by country. In the United States, if the total number of individuals affected by a disease or disorder is less than 200,000—which equates to a prevalence rate of

approximately 6.4 cases per 10,000 citizens–then it is considered a rare disease.[1] By contrast, a disorder or disease is considered rare in the United Kingdom if it affects less than 50,000 individuals.[2]

In the United States, it is estimated that 25 to 30 million people are afflicted with a rare disease, or approximately 8% to 10% of the population. Worldwide, it is estimated that 350 million people suffer from a rare disease. If all of these affected individuals were from a single country, it would be the third most populous country in the world. Rare diseases also account for 35% of all deaths during the first year of life, with children representing approximately 50% of patients with a rare disease. The devastating fact for this patient population is that 30% will not live to see their 5th birthday.[2]

There are now more than 7000 rare diseases recognized by the various organizations and governmental agencies that track, provide support, and coordinate research for the diagnosis and treatment of these disorders and diseases. However, a small number of these rare diseases (approximately 350) account for approximately 80% of the total number of patients affected.[2]

Although rare diseases vary widely in their clinical symptoms and disease progression, most have a strong genetic basis in common. Approximately 80% of rare diseases are caused by a genetic defect, and these diseases are often categorized according to their clinical system impact.[4] Gastrointestinal disorders account for 33%; oncologic, 17%; hematologic, 17%; neurologic, 8%; and rheumatologic, 8% of rare diseases. Other clinical system impacts account for the remaining 17%, and include cardiovascular, endocrine, infectious, lysosomal, musculoskeletal, renal, and respiratory disorders.[1]

Although it is useful to discuss rare diseases in aggregated terms, the reality is that, like common adult and pediatric acute and chronic diseases, prevalence rates vary widely among rare diseases. For example, a relatively well-known rare disease, cystic fibrosis, affects approximately 30,000 individuals in the United States, well below the 200,000 threshold limit, but still representing a substantial number of patients. At the other end of the spectrum are rare diseases, such as paroxysmal nocturnal hemoglobinuria, in which red blood cells breakdown prematurely: less than 500 patients in the United States are estimated to suffer from this disorder. Thus, the key for physicians and other caregivers is to recognize that while aggregate statistics are helpful in understanding the overall problem, they do little to assist with the diagnosis, management, and treatment of the specific rare disease, let alone the psychosocial and economic impacts.

PRACTICAL IMPLICATIONS

In view of the thousands of identified rare diseases and concurrent acceleration of orphan drug development and approvals, healthcare organizations and payers should consider the development of a rare disease strategy and management program. The elements of this program should be designed with input from all affected stakeholders (ie, patients, family members, caregivers, providers, healthcare organizations, payers, etc) and address:

- aggregation, coordination, and access to validated diagnosis, treatment, and maintenance, as well as longer-term prognosis information
- psychosocial impacts
- economic impacts

A program that targets these elements could help to improve the health and well-being of this patient population, in addition to minimizing healthcare resource misapplication and utilization waste.

Drug Development History and Status

The treatment of rare diseases, like common diseases, generally falls into 1 of 3 strategies. For congenital anomalies and other similar physical organ or structure defects, surgery may be an option. Diet and lifestyle changes may also be used to mitigate symptoms or disease impact or progression in a limited number of rare diseases. Overwhelmingly, however, the discovery, development, and use of pharmaceutical agents to provide curative, disease-modifying, and/or symptom and function-modifying relief for patients with rare diseases continues to be a significant area of focus.

Prior to the 1980s, pharmaceutical manufacturers focused their attention on acute and chronic disease states that affected millions of patients. For example, it is currently estimated that in the United States, kidney disease has one of the smaller patient populations, at approximately 4.5 million.[1,3] At the other end of the spectrum, cancer, cardiovascular disease, and diabetes consist of approximately 20, 28, and 29 million US patients, respectively. Hypertension tops the list at 75 million Americans. One can easily see the market potential and financial incentive alignment for drug manufacturers during these decades.

The passage of the Orphan Drug Act in 1983, which provided significant financial incentives consisting of market exclusivity, tax incentives for certain R&D costs, user fee waivers, and "fast track" review by the FDA, began to change the landscape considerably for pharmaceutical manufacturers.[7] Prior to the act, only 38 drugs (now known as orphan drugs) for rare diseases received FDA approval. By contrast, in 2014 and 2015, 47 and 41 new drug entities, respectively, were approved for rare diseases.[1,8] Today, a total of 552 orphan drug products are FDA-approved, with 233 approved in the last decade alone.[9] Further, since

1983, the FDA has designated more than 3600 molecular entities as qualifying for orphan drug status, with a record 422 applications received in 2015.[9] As of 2014, there were more than 450 compounds being actively studied for further development.[1] But even with all of this activity, most rare diseases currently do not have therapeutic drugs that are commercially available for treatment.

The Orphan Drug Act did not modify the historical FDA requirements for drug review and approvals, even given the fast track approval process.[6] Dating back to the 1962 Food, Drug, and Cosmetic Act, the FDA must ensure that there is substantial evidence of clinical efficacy demonstrated through "adequate and well-controlled" clinical trials, in addition to assuring the overall safety of drugs from a risk-and-benefit-analysis perspective. However, 2 key events in the late 1980s and late 1990s clarified the FDA's potential flexibility in reviewing all drugs, especially those for rare diseases. In 1988, the HIV/AIDS crisis lead to the development of IND Subpart E of the Food and Drug Chapter in Title 21, which focused on expediting the development, evaluation, and marketing of "Drugs Intended to Treat Life Threatening Illnesses and Severely Debilitating Illnesses."[10] In addition, in 1998, the FDA issued seminal guidance on "Providing Clinical Evidence of Effectiveness," which delineated 9 different methods in which a single clinical trial could be used to file for drug approval versus the historical requirement of 2 clinical trials. A recent review of the FDA's use of this flexibility in reviewing orphan drugs for approval noted a favorable response in terms of the unique limitations often found in rare disease clinical trials (eg, limited numbers of patients, longitudinal safety monitoring, etc) compared with "common" disease state drug trials.[6]

It is clear that the development of orphan drugs for rare disease states is regarded by several observers of the pharmaceutical industry as the next major market opportunity for drug manufacturers and shareholders, as the markets for common disease drugs plateau.[3] Unlike so-called lifestyle and other similar drugs, well-defined and agreed-upon clinical disorders and diseases exist for rare diseases and do not require convincing providers and payers that there is a need to treat a newly discovered, and often vaguely described, syndrome. There is a readily identifiable target patient population and provider base, which, although dispersed, does not require the marketing investment of historical drug launches. Combined with the now all too common pricing of at least $100,000 in annual drug therapy costs, or multiples thereof, paid predominantly by commercial insurers and government programs, the business potential for rare disease drugs is extremely high.[3]

Impacts on Patients and Caregivers

The impact of a rare disease on a patient and their family and friends can be devastating from a health, psychosocial, and economic perspective. The path to an accurate diagnosis is often very lengthy: an average of 7.6 years in the United States.[1] Depending on the specific rare disease and its clinical manifestations, this can range from just a few months to several decades. Along the way, patients experience an average of 2 to 3 misdiagnoses from an average of 4 primary care physicians and 4 specialists, usually with conflicting treatment advice and disease state information. Patients often have difficulty finding a doctor who is knowledgeable about their specific rare disease and typically wind up educating their provider about their disease history, progress, maintenance, and treatment.[1,5] Patients may need to travel significant distances in order to be seen by a physician with the specific rare disease state knowledge and expertise they need.

The vast majority of patients with a rare disease often experience significant depression (75%), anxiety, and stress (86%); reduced interactions or isolation from family and friends (70% and 65%, respectively), and worry based on lack of information about their disease (90%) and future prognosis (83%).[5] Family and friends serving as caregivers report very similar symptoms and percentages as the patients. The ability to connect with other patients and support groups for a specific rare disease, which is so essential in other common disease states to manage psychosocial concerns, is often limited or very difficult due to the limited numbers of patients within a geographic area or in aggregate. Likewise, the ability to access trustworthy information regarding their disease state online, or elsewhere, is often a challenge. Finally, quality-of-life scores for patients with rare diseases are typically 10% to 20% lower than for common disease state patients and are often reported at less than 50%.[5]

The economic consequences for patients with rare diseases can also be considerable. The ability of the patient and the caregiver to continue working in their chosen field, or elsewhere, may be significantly compromised, if not eliminated, in order to manage the rare disease impact on the patient's and family's lives.[5] Lack of insurance coverage and uncertainty regarding covered therapies and procedures can lead to additional significant financial burdens on the patient and their family. As noted previously, rare disease drug therapies are expensive, easily running into 6 figures on an annual basis. Fortunately, for these patients in particular, the Affordable Care Act eliminated upper coverage limits and pre-existing disease clauses and forced the coverage of routine costs associated with clinical trials. Still, 55% of these

patients have incurred direct medical expenses, and one-third of these patients have borrowed money from family members and friends to pay for their rare disease treatments and maintenance therapies.[5]

Impacts on Providers

Physicians are confronted with a variety of challenges in treating patients with rare diseases. As mentioned previously, the pathway to an accurate diagnosis is often lengthy and filled with conflicting information and misdiagnosis. The root cause of this is the small number of patients a physician may see with a specific rare disease in order to build his or her personal knowledge and experience base in treating these individuals. Combined with the usual education, training processes, and practice experience of physicians of routinely seeing patients with common diseases, the potential for initial and subsequent misdiagnoses is understandable. This phenomenon is frequently described as "the horse and zebra problem."[1] If a rancher hears hoof beats, they assume it is a horse not a zebra, and they are correct more than 99.9% of the time. Fortunately, for ranchers, a quick visual check can immediately remedy their conclusion about what they are dealing with. With physicians and patients with rare disease, the clinical symptoms presented may not be so unique and discerning.

Physicians may also be frustrated about the lack of readily available information, diagnosis, and treatment guidelines in order to enable them to effectively manage patients with rare diseases. Identifying and connecting with other physicians knowledgeable in the specific disease area may be as difficult for providers as it can be for patients. In fact, more than 50% of all rare diseases have no disease-specific foundation or organization that can provide research updates, treatment guidelines, or medical education for providers.[1,5]

The uncertainty regarding disease progression, short- and long-term prognoses, and the unknown impact of long-term drug therapy treatment outcomes and side effects can also be major concerns for physicians and patients. Finally, the psychosocial impact and economic concerns and stresses of the patient, family members, and caregivers can be challenging for physicians and other healthcare providers to manage.

Clearly, all of these factors can take a toll on a physician professionally and personally and from a practice management perspective. Patients with rare diseases have more frequent office visits and, in general, consume more time during an office visit due to the uncertain nature of their diagnosis and disease management.[5] Also, coding for billing reimbursement and management of receivable claims is more labor-intensive due to the infrequency of submission and, often, the inadequacy or lack of treatment and payment guidelines. Additionally, physicians may have to spend a disproportionate amount of their own continuing education time becoming further educated on rare diseases versus keeping up with the more common acute ailments and chronic disease states seen in the vast majority of their practices.

Impacts on Healthcare Organizations/Payers

The consumption of provider and ancillary resources as the patient with a rare disease attempts to get an accurate diagnosis and subsequent treatments is a significant drain on both healthcare organization resources and payer budgets. Compared with more common ailments and diseases, patients with rare diseases undergo approximately twice the amount of diagnostic tests and have specialist visits at approximately twice the cost of other patients in a health plan.[5] Furthermore, due to psychosocial stresses, patients with rare diseases incur approximately 90% more mental health support services than patients with more common disorders and diseases. As mentioned previously, the difficulty of diagnosis and the lack of evidence-based standards or guidelines for treatment protocols may often result in payor reluctance to reimburse provider and patient costs. Finally, as mentioned previously, the lack of significant patient population history regarding specific rare disease progression and prognosis makes projecting cost impacts and resulting insurance premiums difficult, at best.

Additionally, due to the low incidence of rare diseases, most hospitals and health systems do not have a defined proactive strategy in place regarding management of these patients, including formulary management of the new medications available. Although expensive, many of these medications represent good value in terms of better managing these patients and reducing overall costs of care. However, the perspective must be from the long-term care of these patients. An episodic consideration once a patient appears, and the expensive therapy that is required, is not the best approach.

Summary

Patients with rare diseases present a unique challenge to the current healthcare system when you consider their diagnosis, treatment, and prognosis status. The development and implementation of a rare disease management strategy at a provider and/or healthcare organizational level could provide significant benefits to this patient population. As noted in a recent report, there is a greater need for collaboration amongst the various stakeholders, including patients, family members, caregivers, physicians, other providers, and payers, on both a domestic and global basis.[5]

The need for aggregation, access, validation and communication of known disease state diagnoses, treatment, and maintenance information is a critical element in improving care for these patients. The collection and coordination of patient data through patient registries and research studies is critical to better understanding specific rare disease diagnoses and prognoses, as well as the development of effective primary and supportive treatment options.

Increased coordination of care and communication of patients' symptoms, status, and concerns among providers could expedite patient rare disease state diagnosis, treatment, and/or management and potentially mitigate the known psychosocial impacts of a rare disease diagnosis. Finally, healthcare organizations and payers could benefit from a reduction in healthcare resource misapplication and/or utilization waste, along with mitigating patient economic impacts.

Addressing all of these issues with an overall rare disease management strategy and within a specific rare disease state is essential in order to make further positive progress for these patients.

REFERENCES

1. Rare Disease Resource Guide. *Rare Disease Report* website. http://www.raredr.com/resource-guide. Accessed July 8, 2016.
2. Rare Diseases: Facts and Statistics. Global Genes website. www.globalgenes.org/rare-diseases-facts-statistics/. Accessed July 8, 2016
3. Herper, M. The World's Most Expensive Drugs. *Forbes* website. http://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rare-diseases.html. Published February 22, 2010. Accessed July 8, 2016.
4. Genetic and Rare Diseases Information Center. National Institutes of Health website. www.rarediseases.info.nih.gov/gard/categories. Accessed July 8, 2016.
5. Shire. *Rare Disease Impact Report: Insights from patients and the medical community*. www.globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf. Published April 2013. Accessed July 8, 2016.
6. Sasinowski, F. National Organization for Rare Disorders. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs; 2011. www.nordphysicianguides.org/wp-content/uploads/2012/02/NORD-study-of-FDA-approval-of-orphan-drugs.pdf. Accessed July 8, 2016.
7. US Centers for Disease Control and Prevention. FastStats – Statistics by Topic. CDC website. www.cdc.gov/nchs/fastats. Accessed July 8, 2016.
8. PhRMA. A Decade of Innovation in Rare Diseases; 2015. http://www.phrma.org/sites/default/files/pdf/PhRMA-Decade-of-Innovation-Rare-Diseases.pdf. Accessed July 9, 2016.
9. Silverman, E. FDA designated a record number of orphan drugs last year. *Pharmalot* website. www.statnews.com/pharmalot/2016/02/11/fda-designates-record-number-of-orphan-drugs. Published February 11, 2016. Accessed July 9, 2016.
10. Food and Drug Administration. Code of Federal Regulations Title 21; 2015. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.5 Accessed July 10, 2016. ajpb