CHEST

The Challenge of Rare Diseases

James K. Stoller, MD

Rare diseases pose particular challenges to patients who are affected, to the clinicians who care for them, and to the investigators who study their conditions. Although individually uncommon, rare diseases are common in the aggregate, with approximately 7,000 described rare diseases affecting 25 to 30 million US adults. Challenges posed to affected individuals and their families largely regard being diagnosed, receiving optimal care, and affording disease-specific medications. Challenges facing clinicians who care for affected individuals include gaining knowledge and experience in caring for such patients, and the availability of local experts and of expert guidelines. Finally, challenges to investigators regard the difficulty and expense of assembling large cohorts of affected individuals for study, and garnering funding for research. Fortunately, in the face of these challenges, the steadfast resolve of patient and clinical/scientific communities to enhance care and generate new knowledge has fostered a large inventory of countermeasures to offset these challenges. Although further progress is surely needed, successes to date include the formation of powerful patient advocacy groups which have brokered collaborations between the patient, scientific communities, the government, and pharma/device communities in service of detection, optimal care, and research; procurement of funds to support research; formation of consortia of clinicians and scientists to collaborate; and general activation of the respective patient communities to perpetuate these successes. Persisting needs include enhanced detection strategies, dissemination of knowledge regarding optimal care, and research to prevent, treat, and cure disease. CHEST 2018; 153(6):1309-1314

KEY WORDS: alpha-1 antitrypsin deficiency; lymphangioleiomyomatosis; rare disease

Rare diseases pose special challenges which impact patients, the clinicians who care for them, and the investigators who study their conditions. Although rare diseases—defined as affecting < 200,000 US adults[1]—are individually uncommon, they are common in the aggregate, with nearly 7,000 such rare diseases affecting 25 to 30 million US adults, altogether 9% to 12% of the US population.[1] Rare pulmonary diseases comprise an important subset and include, for example, alpha-1 antitrypsin deficiency (AATD), primary ciliary dyskinesia, lymphangioleiomyomatosis (LAM), Hermansky-Pudlak syndrome, Birt-Hogg-Dube syndrome, pulmonary Langerhans cell histiocytosis, and hereditary hemorrhagic telangiectasia, among many others.

The challenge of these rare diseases is captured in the names of organizations charged with their oversight, that is; the branch of the Food and Drug Administration that oversees rare disease treatments is called the Office of Orphan Products Development, the designated group

ABBREVIATIONS: AATD = alpha-1 antitrypsin deficiency; HHT = hereditary hemorrhagic telangiectasia; LAM = lymphangioleiomyomatosis

AFFILIATIONS: From the Cleveland Clinic, Cleveland, OH.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: James K. Stoller, MD, 9500 Euclid Ave, NA22, Cleveland, OH 44195; e-mail: stollej@ccf.org

DOI: https://doi.org/10.1016/j.chest.2017.12.018

of the National Institutes of Health is called the Office of Rare Diseases, and the legislation that directs regulatory requirements for drugs and devices for these conditions is called the Orphan Disease Act. Orphan diseases may lack support and advocacy just as orphans lack parents.

This perspective piece considers the challenges posed by rare diseases through three lenses: the challenges for patients with a rare disease, the challenges for clinicians who care for them, and the challenges for investigators who study their diseases. In considering each of these issues, I submit that generalizable observations emerge from experience with AATD, an important rare disease for which substantial progress has been made since its description in 1963.[2] After considering the challenges, I review countermeasures to offset these challenges and some of the successes born by these measures to date.

Challenges to Patients

The challenges to patients with a rare disease are threefold: they may experience the manifestations of the disease but struggle to find physicians knowledgeable about their condition to manage them; they may suffer the consequences of the disease and go completely unrecognized; and they may be faced with very high costs for disease-specific medications.

Lessons from AATD amply demonstrate all three phenomena. First, of the estimated 100,000 US adults with severe deficiency of alpha-1 antitrypsin, < 10,000 have been recognized.[3,4] Such underrecognition appears to be a global problem, similarly observed in every country in which the issue has been examined.[5] Furthermore, patients with AATD often experience long delays between their first attributable symptom and initial diagnosis (frequently called the diagnostic delay interval). Multiple series between 1995 and 2013[6-9] report a persisting diagnostic delay interval of 7 to 8 years for individuals with AATD. Compounding this delay is the fact that patients with AATD commonly see multiple physicians with AATD-attributable symptoms before the diagnosis is initially made. In one series,[6] 43% of patients with AATD reported seeing at least three physicians before initial diagnosis, and 12% reported seeing between six and 10 physicians.

Because AATD is a progressive disease that is associated with accelerated loss of lung function[9] and emphysema progression,[10] it is logical to presume that delayed diagnosis is associated with adverse clinical sequelae, and more specifically, that patients who present with longer diagnostic delays have more advanced disease with a greater symptom burden at the time of initial diagnosis. Strangely, there is a paucity of evidence supporting this contention because few studies have examined this question. Recent preliminary data from Tejwani et al[11] do support the observation; individuals with AATD who presented with longer diagnostic delays tended to have lower FEV_1 % predicted, and had significantly worse functional status and symptoms at the time of presentation (demonstrated by higher St. George's Respiratory Questionnaire and COPD Assessment Test scores) than patients who experienced shorter diagnostic delay intervals.

Finally, the cost of augmentation therapy for AATD, the infusion of purified pooled human plasma-derived alpha-1 antitrypsin, which is the only specific medication currently available for patients with AATD-associated emphysema, is very high, with costs seemingly increasing with successive new entries. Four augmentation therapy drugs have been approved by the US Food and Drug Administration to date. Recognizing that for beneficiaries of insurance, the bulk of the cost of the drug is born by the insurer, the average wholesale price for the four augmentation therapy drugs in 2017 ranges from $0.59 to $0.62/mg; for a 70-kg man receiving the recommended dose of 60 mg/kg once weekly, this translates to a yearly cost of $128,856 to $135,408. Patients with high deductible plans will surely erode their deductibles on these medications alone, and those without insurance find the medications unaffordable. Regrettably, the high cost of drugs for AATD is not atypical for rare lung disease treatments. As another example, the 2017 average wholesale price for rapamycin for LAM is $31.50 for a 2-mg tablet; therefore, a patient with LAM taking 2 mg/d will incur a yearly cost of $11,497.50. Clearly, patients with rare disease face high drug costs.

Challenges to Clinicians Who Care for Individuals With Rare Diseases

The challenges to clinicians who care for such patients mirror their patients' experience. Characteristically, in rare diseases, knowledge and experience with managing such diseases are concentrated in those (usually relatively few) dispersed centers where clinicians have taken special interest and have developed deep experience with these conditions. Understandably, a clinician's expertise in managing a disease is proportional to the frequency with which he/she encounters and manages patients with the disease. In the case of AATD, most pulmonary physicians may see and

manage only a handful of such patients over a career. In keeping with the notion that clinicians' experience caring for patients with rare diseases may be thin, Greulich et al.[8] reported that clinicians' self-reported knowledge of the lung disease associated with AATD was low. Specifically, in surveying Italian and German pulmonologists, internists, and general practitioners regarding the question "How much do you know about lung disease caused by AATD?," 38% and 8%, respectively, of German pulmonologists reported a little or none at all, and 46% and 18%, respectively, of Italian general practitioners reported similarly.[8] Recognizing that the physicians' actual knowledge base could be less than was reported in study survey responses, these data underscore a challenge associated with rare diseases. Furthermore, Taliercio et al.[12] assessed internal medicine residents' knowledge of AATD with a simple survey and reported that the mean rate of correct responses was 54.3%, without evidence that senior residents performed better than interns. Taken together, these data demonstrate a knowledge gap regarding AATD that likely generalizes broadly to many other rare diseases.

This knowledge gap in rare diseases is compounded by the limited availability of official guidelines that are invited and endorsed by official societies. In the case of AATD, four guidelines regarding the management of AATD have been published in North America since 1989,[13-16] when the American Thoracic Society issued the first such document. Notwithstanding the American Thoracic Society's commissioning and endorsing a 2003 standards document that was codeveloped by the European Respiratory Society and also endorsed by the American College of Chest Physicians (CHEST) and the American Association for Respiratory Care,[14] attempts to update this document more recently as an endorsed guideline were hampered by some society policies that preclude participation in guideline writing committees by authors with any perceived industry collaborations. For rare diseases in which clinical and investigative experience is concentrated in few centers and for which progress is often enhanced by collaboration between all stakeholder communities (ie, patients, government, pharma, clinicians, scientists), the availability of experts with no engagement with patient advocacy organizations or any industry ties that would permit their participation in drafting guidelines may be sparse or nil.

Another challenge shared by clinicians and patients is that centers with deep expertise are frequently geographically dispersed, requiring patients to travel long distances for care or foregoing travel if the expense of travel or going out of an insurance network precludes such visits.[1] In the Alpha-1 Registry that is supported by the Alpha-1 Foundation,[17,18] a disproportionate number of all registry participants with severe deficiency of alpha-1 antitrypsin (eg, PI*ZZ) were seen in only a relatively few clinical centers. As another example, the Hereditary Hemorrhagic Telangiectasia (HHT) Foundation[19] lists only four HHT clinical centers in Canada and 22 centers located in 18 states in the United States.

Taken together, rare diseases pose challenges for clinicians and patients alike that converge on the regrettable truth that the availability of and access to expert care may be limited.

Finally, rare diseases pose challenges for investigators who wish to focus on these clinical problems.

Challenges to Investigators Studying Rare Diseases

Three main issues comprise the challenges to investigators who wish to study rare diseases: (1) assembling cohorts of patients for clinical study is challenging and invariably requires prolonged (and therefore expensive) multicenter collaborations; (2) although expedited regulatory approval has clear benefits, the availability of drugs or devices by expedited approval mechanisms[1] understandably challenges equipoise in the patient and physician communities, thereby hampering recruitment to subsequent randomized, placebo-controlled treatment trials when required; and (3) funding for research on rare diseases is commonly sparse.

In the first challenge, in the context of their rarity, studying rare diseases requires prolonged, multicenter collaborations. As an example, in AATD, accrual over 3.5 years was required to recruit 1,129 subjects in 37 centers to the National Institutes of Health Registry for Patients with Severe Deficiency of Alpha-1 Antitrypsin.[9] Almost 20 years later, 4.5 years of active recruitment was required to accrue 180 subjects from 152 centers in 13 countries to conduct the so-called RAPID trial,[10] a randomized placebo-controlled trial of intravenous augmentation therapy. Underscoring the challenge of recruitment to placebo-controlled trials in countries where drugs are available, only 9.5% of the 180 subjects in the RAPID trial were recruited from the centers in the United States,[10] where the first augmentation therapy drug received regulatory approval in 1987.

The second challenge facing investigators of rare diseases represents both an advantage and a challenge. On the one hand, the Orphan Drug Act facilitates fast-track approval of therapies for rare diseases or diseases for which "there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug."[20] On this basis, treatments for rare diseases may gain regulatory approval with smaller and simpler studies than might otherwise be required. For example, all four pooled human plasma-derived alpha-1 antitrypsin preparations for intravenous augmentation therapy received initial approval on the basis of biochemical efficacy without early evidence that augmentation therapy slowed the rate of emphysema progression. However, partially offsetting this obvious advantage is that, as previously discussed for the RAPID trial,[10] recruitment for subsequent placebo-controlled trials to better understand clinical efficacy is hampered by potential lack of equipoise by patients and physicians in countries where the drug has already received regulatory approval for use. Similarly, recruitment to subsequent postmarketing studies that may be required by regulatory agencies is likely to be very challenging because patients receiving augmentation therapy and their physicians may understandably be reluctant to forego available treatment to participate in placebo-controlled trials.

The third challenge facing investigators of rare diseases is that sources of funds and the magnitude of funding for rare disease research may be disproportionately limited. As an example, as of 2009, the annual budget for orphan product development grants in the Office of Orphan Products Development totaled $14 million.[1] The relative paucity of funds requires investigators to seek novel funding mechanisms, such as through philanthropy or engaging with patient advocacy organizations. These groups are often highly focused on garnering support for research from the stakeholder patient communities, and grantseeking from pharma or device manufacturers and from venture philanthropy sources.

Proposed Solutions and Selected Successes to Optimize the Care of Patients With Rare Diseases and to Advance Cures

In the context of the many challenges posed by rare diseases to patients, clinicians, and investigators alike, what potential solutions exist? Fortunately, the plethora of such conditions and the steadfast resolve of patient and clinical/scientific communities to enhance care and generate new knowledge have fostered a broad inventory of countermeasures to offset these challenges and their associated potential adverse effects. Equally fortunate is that this resolve and these countermeasures have produced some noteworthy successes to date.

Foremost among these countermeasures is the emergence of patient advocacy organizations that can organize and rally patient communities. Such advocacy organizations have brokered relationships between the clinical, scientific, governmental, and pharma/device communities in service of supporting research to find cures and ameliorating disease impact. Premier examples of such pulmonary-related patient advocacy organizations include the Alpha-1 Foundation,[18] the Cystic Fibrosis Foundation, the LAM Foundation, the National Organization for Rare Disorders, the Hermansky-Pudlak Syndrome Network, and the HHT Foundation,[19] among others. Each of these organizations is intensely focused on brokering and advocacy. As examples, the mission of the Alpha-1 Foundation is "finding a cure for alpha-1 antitrypsin deficiency and…improving the lives of people affected by Alpha-1 worldwide." The HHT Foundation cites "one mission that drives everything we do – to find a cure for HHT disease."[19]

Metrics of success of these organizations include their fundraising for research and grantmaking; their promoting conferences regarding key issues that assemble experts, patients, government, and industry to explore solutions (eg, Gordon L. Snider Critical Issues Workshop series in AATD); and their providing much-needed resources for clinical care and patient support through Clinical Resource Center networks and patient support groups. In general, such organizations give voice to patients—sometimes self-referring as impatient patients (J. W. Walsh, personal communication, 2009)[21]—to offset the inattention that having a rare disease can incur. To enhance access to care for specialists who are geographically dispersed, patient advocacy groups may issue travel awards to patients so that they may see experts in their care or attend national conferences so that they may self-educate and network with other affected individuals. Similarly, to facilitate access to experts when distance precludes a face-to-face appointment, leading health-care institutions are increasingly providing electronic consultations where experts can review submitted medical records and offer opinions to patients and their local physicians. Also,

virtual Skype-like follow-up visits are being offered to check on patients' progress.

A core benefit of patient advocacy organizations is their developing a community of activated patients.[22] Activated patients can develop transcendent strategies to cope with their conditions and, in my experience, manage their illnesses more successfully and with better clinical outcomes. Activated patients also contribute to collaborative self-management which can enhance care.[23] For example, a cross-sectional analysis of patient activation in a primary care population showed that patient activation was associated with benefit in 12 of the 13 outcomes examined, including fewer ED visits, a lower prevalence of obesity, and lower prevalence of smoking.[22]

Another countermeasure to offset the scarcity of funding for rare disease research is the creation of funds and mechanisms that are earmarked for rare disease research and that encourage the assembly of consortia to conduct such research. Important examples of both include the Orphan Drug Development Grant program of the Food and Drug Administration[1,24] and the Rare Diseases Clinical Research Network of the National Institutes of Health's National Center for Advancing Translational Sciences.[25] Specifically, the Rare Lung Diseases Consortium of the National Center for Advancing Translational Sciences is a consortium of clinical centers and the National Institutes of Health that has provided a much-needed focus on LAM, pulmonary alveolar proteinosis, Hermansky-Pudlak syndrome, Birt-Hogg-Dube syndrome, and pulmonary Langerhans cell histiocytosis, with clinical centers of expertise, academic research collaborations, and funding opportunities. In the specific case of LAM, selected triumphs of patient advocacy and these consortia have included the following: the organization of annual LAMposium which assembles scientists, clinicians, and patients; the LAM Clinics Network of 33 clinical centers in the United States and 25 internationally; completion of clinical trials of sirolimus; and subsequent petitioning of the Food and Drug Administration for LAM indication approval.

Similarly, patient advocacy organizations issue grants to support research. As a noteworthy example among others, since its inception in 1995, the Alpha-1 Foundation has issued grants totaling $65 million to a total of 112 investigators in 106 institutions in North America, Europe, the Middle East, and Australia. Similarly, the LAM Foundation has successfully raised money for research and for career awards to clinician-scientists in concert with the Rare Lung Disease Consortium. Although more funding is needed for all rare diseases, these patient organizations and consortia help aggregate talent, can help direct funds for research, and create networks of investigators who can share and accelerate progress through collaboration.

Overall, although having a rare disease poses various challenges, the resilience and creativity of the patient and governmental, scientific, and commercial stakeholders have created powerful offsetting mechanisms by which care has been made available and research toward cures has advanced. Current imperatives include further activating the stakeholder patient communities and aligning goals between patients, the government, the clinical/scientific communities, and pharma/device manufacturers; driving early detection of affected individuals to allow access to optimal current care and future research opportunities; and enhancing awareness and knowledge of rare diseases among clinicians, including both specialty and primary care physicians and allied health and advanced practice providers who see these patients, and advancing research toward curing these diseases. Key to achieving these goals is that novel detection and educational strategies directed at frontline caregivers[26,27] are critically needed.

Acknowledgments

Author contributions: J. K. S. is solely responsible for the entire content of this paper.

Financial/nonfinancial disclosures: The author has reported to *CHEST* the following: J. K. S. serves as a consultant to CSL-Behring, Shire, Grifols, Arrowhead Pharmaceuticals, Vertex, and 23andMe regarding alpha-1 antitrypsin deficiency. J. K. S. serves as a member of the Board of Directors of the Alpha-1 Foundation.

References

1. Griggs RC, Batshaw M, Dunkle M, et al. Clinical research for rare disease: opportunities, challenges, and solutions. *Mol Genet Metab*. 2009;96(1):20-26.
2. Stoller JK, Aboussouan LS. A review of alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med*. 2012;185(3):246-259.
3. Aboussouan LS, Stoller JK. Detection of alpha-1 antitrypsin deficiency: a review. *Respir Med*. 2009;103(3):335-341.
4. Stoller JK, Brantly M. The challenge of detecting alpha-1 antitrypsin deficiency. *COPD*. 2013;10 suppl 1:26-34.
5. Luisetti M, Seersholm N. Alpha1-antitrypsin deficiency. 1: Epidemiology of alpha1-antitrypsin deficiency. *Thorax*. 2004;59(2):164-169.
6. Stoller JK, Smith P, Yang P, Spray J. Physical and social impact of alpha 1-antitrypsin deficiency: results of a survey. *Cleve Clin J Med*. 1994;61(6):461-467.
7. Stoller JK, Sandhaus RA, Turino G, Dickson R, Rodgers K, Strange C. Delay in diagnosis of alpha1-antitrypsin deficiency: a continuing problem. *Chest*. 2005;128(4):1989-1994.

8. Greulich T, Ottaviani S, Bals R, et al. Alpha1-antitrypsin deficiency - diagnostic testing and disease awareness in Germany and Italy. *Respir Med*. 2013;107(9):1400-1408.

9. McElvaney NG, Stoller JK, Buist AS, et al. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of alpha 1-antitrypsin deficiency. Alpha 1-Antitrypsin Deficiency Registry Study Group. *Chest*. 1997;111(2):394-403.

10. Chapman KR, Burdon JG, Piitulainen E, et al. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;386(9991):360-368.

11. Tejwani V NA, Fye E, Sanders C, Stoller JK. System and airflow correlates of delayed diagnosis in alpha-1 antitrypsin deficiency. Paper presented at American College of Chest Physicians International Meeting; October 29, 2017; Toronto, ON, Canada.

12. Taliercio RM, Chatburn RL, Stoller JK. Knowledge of alpha-1 antitrypsin deficiency among internal medicine house officers and respiratory therapists: results of a survey. *Respir Care*. 2010;55(3):322-327.

13. Guidelines for the approach to the patient with severe hereditary alpha-1-antitrypsin deficiency. American Thoracic Society. *Am Rev Respir Dis*. 1989;140(5):1494-1497.

14. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of patients with alpha-1 antitrypsin deficiency. Stoller JK (Co-chairman), Snider GL, Brantly ML, Fallat RJ, Stockley RA (Executive Committee). *Am J Respir Crit Care Med*. 2003;168:816-900.

15. Abboud RT, Ford GT, Chapman KR. Alpha1-antitrypsin deficiency: a position statement of the Canadian Thoracic Society. *Can Respir J*. 2001;8(2):81-88.

16. Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. *Can Respir J*. 2012;19(2):109-116.

17. Walsh JW, Snider GL, Stoller JK. A review of the alpha-1 foundation: its formation, impact, and critical success factors. *Respir Care*. 2006;51(5):526-531.

18. Alpha-1 Foundation. www.alpha1.org. Accessed November 5, 2017.

19. HHT Foundation. Directory.curehht.org. Accessed November 19, 2017.

20. U.S. Food and Drug Administration. Orphan Drug Act - relevant excerpts. https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm. Accessed November 5, 2017.

21. Ryde D. Impatient patients. *BMJ*. 1973;3(5881):639-640.

22. Greene J, Hibbard JH. Why does patient activation matter? An examination of the relationships between patient activation and health-related outcomes. *J Gen Intern Med*. 2012;27(5):520-526.

23. Make B. Collaborative self-management strategies for patients with respiratory disease. *Respir Care*. 1994;39(5):566-579.

24. U.S. Food and Drug Administration. Developing products for rare diseases & conditions. https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm. Accessed November 17, 2017.

25. National Center for Advancing Translational Sciences, Rare Diseases Clinical Research Network. www.ncats.nih.gov. Accessed November 5, 2017.

26. Rahaghi FF, Sandhaus RA, Brantly ML, et al. The prevalence of alpha-1 antitrypsin deficiency among patients found to have airflow obstruction. *COPD*. 2012;9(4):352-358.

27. Stoller JK, Strange C, Schwarz L, Kallstrom TJ, Chatburn RL. Detection of alpha-1 antitrypsin deficiency by respiratory therapists: experience with an educational program. *Respir Care*. 2014;59(5):667-672.