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CHEST Commentary

The Many "Small COPDs"*

COPD Should Be an Orphan Disease

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COPD is one of the most common causes of morbidity and mortality. Perhaps paradoxically, COPD also should be an orphan disease. Importantly, this could advance the development of treatments for COPD. There are two criteria for orphan status in the United States. Most widely known is the criterion of < 200,000 affected individuals; however, secondarily, is the impossibility for development costs to be recovered during the patent life of a product. COPD should qualify for the first criterion if the various conditions that comprise COPD are regarded separately. The subphenotyping of COPD into separate groups based on mechanism sets the stage for the rational development of therapeutics. In addition, many candidate treatments may alter the natural history of COPD. Testing them, however, will require large studies for a duration that will compromise the commercial life of any resulting product. Orphan status, therefore, could facilitate the development of treatments for both phenotypic subsets of COPD patients as well as aid the development of agents to alter the natural history of the disease. Post-drug approval regulations could require that agents approved under the orphan provisions are prospectively monitored, assuring that rigorous longitudinal data are generated. This approach could encourage the pharmaceutical industry to stratify studies based on a more detailed characterization of study subjects at baseline, thus approaching "many small COPDs" instead of a single large and heterogeneous COPD. This strategy may help to address the increasing burden that COPD presents and for which no novel clinical class of treatment has been introduced for 30 years.

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Key words: COPD; drug therapy; phenotype

Abbreviations: α_1AT = α_1-antitrypsin; FDA = Food and Drug Administration

COPD is epidemic. It is currently the fourth leading cause of death in the United States affecting perhaps 24 million people, half of whom are undiagnosed.[1] Its prevalence worldwide is increasing, and it is estimated that it will become the third leading cause of death in both the United States and the world as a whole by the year 2020[2]. Nevertheless, according to the current criteria, COPD should be considered an orphan disease. A similar approach could be taken with many common clinically defined disorders; however, only COPD will be addressed here. Importantly, such an approach could lead to the development of more specific and more effective treatments, and could potentially make them available at reduced costs compared to other newly introduced drugs.

Rationale for Orphan Drug Status

The US Food and Drug Administration (FDA) has defined two criteria, either of which qualifies a drug as an orphan.[3] These are as follows:

1. ". . . the disease or condition for which the drug is intended affects fewer than 200,000 people in the United States . . . . " and

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2. ". . . for a drug intended for diseases or conditions affecting 200,000 or more people . . . . there is no reasonable expectation that costs of research and development can be recovered by sales of the drug in the United States."

Similar criteria have been implemented in the European Union.[4] We would argue that treatments for COPD could qualify by both criteria, either of which is sufficient for COPD to be regarded as an orphan disease. This reclassification could be an effective strategy to address this major public health problem, and, at the same time, could potentially help to contain heath-care costs.

Criterion 1 and the Importance of Small Subsets

While COPD affects far more than 200,000 people in the United States, COPD is not a disease in the narrow sense that tuberculosis is. COPD is defined on the basis of a single physiologic parameter, reduced expiratory airflow.[5] In this regard, COPD is more like "fever." Not so long ago, a great variety of diseases would have been classified as a fever, including tuberculosis, plague, Hodgkin disease, and familial Mediterranean fever, among a very large group of diseases, many of which are rare and now qualify as orphan conditions. Without doubt, fevers are more heterogeneous than COPD. Nevertheless, COPD is an extremely heterogeneous disorder. Current concepts suggest that it results from the complex interactions of many genetic factors, most of which remain undefined, that interact with many environmental factors, the most of important of which is cigarette smoking. This etiologic and mechanistic heterogeneity creates both opportunities and problems for the development of rational therapies. For example, inflammation likely plays a key role in the development of COPD. However, in COPD patients, there are several different inflammatory responses that vary qualitatively and quantitatively; it is likely that there are many pathways for their pathogenesis.[6] Many mechanistically based interventions, therefore, are reasonable. Unfortunately, it seems plausible that most will be dramatically effective for a subset of COPD patients, but useless (or worse) for others. The classification of COPD, or at least the determination of definable subsets of COPD patients who share common mechanistic pathways that would be appropriate for a specific intervention as an orphan disease, is appropriate to address this problem.

This line of thinking is not entirely novel. The only specific genetic disorder that unambiguously causes COPD is α_1-antitrypsin (α_1AT) deficiency, which accounts for about 2% of cases of emphysema in the United States.[7] Importantly, the only criterion that is used to define this subset of patients is a biomarker, the α_1AT level. The clinical features of COPD, which can be characteristic of α_1AT, are not useful in this regard as they represent a continuum that overlaps and merges with the remainder of the COPD population (and healthy population). Based on this biomarker, α_1AT replacement therapy has been approved by the FDA under the Orphan Drug Act. How many subsets of COPD might be recognizable as tractable clinical entities and how many of them may affect $<$ 200,000 individuals in the United States remains to be defined. Nevertheless, it seems likely that many genetic diseases that are less common than α_1AT deficiency would qualify. In addition, there is a large number of biomarkers other than α_1AT as well as clinical features that could be used to segregate COPD patients[8,9] that may also meet the criterion for orphan status.

An interesting example of the potential to define orphan subsets of COPD patients is offered by the recent evaluation of anti-tumor necrosis factor antibodies. Two trials were initiated. In the first trial, COPD patients who were defined based on FEV_1 were assessed. The results were clear. No clinical benefit was found for the active antibody, either compared to placebo or to the subject baseline.[10] A suggestion of benefit was observed in the subset of subjects who were cachectic, but the study was not powered to draw conclusions about this group. Because it was plausible that cachectic individuals might particularly benefit from anti-tumor necrosis factor antibody treatment, a separate parallel study was conducted, but unfortunately enrolled very few subjects and was terminated. The subset of cachectic COPD patients, depending on its definition, might qualify as an orphan group. As cachexia has a particularly poor prognosis in COPD patients, approval under orphan status could make a potentially life-saving therapy available that would be otherwise impossible to register.

Approval of a drug under orphan status can also facilitate further evaluation of the drug. The approval of the α_1AT biomarker, for example, was contingent on the establishment of a registry database. This provided important longitudinal information in individuals receiving and not receiving replacement therapy. Postmarketing requirements for the use of an orphan product, however, could also include proscribed diagnostic studies. A registry database can provide important information on the effect of a novel medication through observational studies. Although not as compelling as prospectively randomized and controlled studies, carefully conducted

observational studies of defined interventions have the potential to provide information of tremendous importance for a relentlessly progressive disorder such as COPD.[11]

Criterion 2 and "Expensive" Studies of COPD Natural History

COPD as currently defined is not rare, and there is a legitimate rationale to group COPD patients together. While many different genetic and environmental factors, the most important of which is cigarette smoking, and clinical features of COPD can vary dramatically from patient to patient, some features, such as the progressive loss of lung function, are common. A treatment that would slow this progression of the disease could benefit a very large number of patients. However, according to criterion 2, even if such a treatment benefited all COPD patients, COPD should probably still be regarded as an orphan disease.

The reason for this seeming contradiction is the fact that a disease also qualifies for orphan status if there is "no reasonable expectation that the costs of research and development. . . can be recovered from sales of the drug in the United States."[3] This should apply to treatments targeting disease progression in COPD patients. The progression of COPD is currently measured by a decline in expiratory airflow, specifically by a decrease in FEV_1. Fortunately for the COPD patient, and unfortunately for the developers of potential COPD treatments, the rate at which the FEV_1 is lost is slow and variable. Although the rate increases with age, it averages about 60 mL/year in patients who have a current diagnosis of COPD, but is much less in undiagnosed patients who nevertheless experience increased mortality. This rate of decline in FEV_1 contrasts with a rate of 25 to 30 mL/year in healthy individuals.[12] While the FEV_1 is the best measure of airflow, the variance in the measure is 55 mL, at best. The measurement of FEV_1 is a highly mature technology, and it is unlikely that this variance will improve. As a result, any clinical trial designed to improve the rate of decline in lung function will require a large number of subjects who are followed up for relatively long periods of time. Anthonisen et al[13] calculated that an intervention that reduced the increased rate of decline in COPD patients by 50% (*ie*, an improvement of 20 mL/year) would require 2,000 to 2,400 patients to be followed up for at least 3 years. Smaller improvements would require even larger and/or longer studies. These large sample size estimates apply to any intervention designed to alter the rate of FEV_1 decline.

Smaller improvements, however, could be lifesaving. At the end stage of the disease, the rate of FEV_1 loss might be as much as 100 mL/year. Thus, as a conservative estimate, a saving of 100 mL could be estimated to be a gain of a year of life expectancy. This estimate, interestingly, is similar to that observed following lung volume reduction surgery. With this assumption, a gain of 5 mL/year, over a 50-year time frame would be 250 mL and might mean an additional 2.5 years of life. The application of such an intervention, of course, would require the early diagnosis of COPD, which is readily practicable with routine spirometry. In 1990, Anthonisen et al[13] estimated the cost of a trial powered to observe a 20-mL benefit in the progression of FEV_1 as the end point to be \$15 to \$20 million plus drug costs in 1991, and this estimate seems extremely optimistic. Two current trials[14,15] in COPD patients that have assessed similar numbers of patients over similar time frames and their costs are likely to exceed the estimate of Anthonisen et al[13] by a factor of 10. Treatments that had smaller benefits, though important, would be much more expensive. As a result of these unforgiving numbers, the development of treatments to mitigate the progression of COPD would likely cost many times that of the billion dollars currently required to bring a drug to market.

The sales of a drug to a population of tens of millions for decades would be very large. However, a minimum duration for a study of the progression of FEV_1 decline is 3 years. This is the duration that would be required for dose ranging in phase 2 and would be required again in phase 3. This long duration of COPD trials would cut seriously into the patent life of any drug that is brought to market. Thus, even though there might be a large and potentially lucrative market, the long duration required for clinical trials of COPD progression make the expectation that the costs of research and development could be recovered by the company that made the investment less reasonable. One way to address this problem would be to extend the patent life for drugs that are developed for this indication. However, the Orphan Drug Act is already in place to address this need. An alternative strategy, to develop an outcome measure that requires smaller studies or shorter study durations, is also possible. In this context, other parameters of COPD also progress. While none have yet been used as measures of disease progression for the purpose of drug registration, emphysema quantification by CT scan may have utility in this regard. Whether it will facilitate the evaluation of novel therapies is, as yet, undefined.

Orphan Status and the Pharmaceutical Industry

Orphan status should not be a way for pharmaceutical companies to reap a windfall by sidestepping

regulatory rules. Rather, by complying with the current rules and by resetting financial expectations, pharmaceutical companies could introduce many new products and benefit in new ways while at least potentially lowering pharmaceutical costs.

Current drug development practice[5,16] regards COPD as a single entity. It is a large market, and subjects for trials can be readily identified using well-established criteria. Pharmaceutical companies are attracted to COPD, at least in part, because of the large size of this market. Unfortunately, going for a "blockbuster" in this market has not resulted in a novel treatment. The only therapies that have been developed and approved for the treatment of COPD as a whole are ones that have a measurable effect, over relatively short time frames, on the defining feature of the overall syndrome (*ie*, airflow limitation as measured by FEV_1). Increasingly large studies[14,15,17] have been carried out with existing therapies including exacerbations and quality of life as end points. Despite demonstrating benefits on these end points, these large trials have taught us disappointingly little about disease mechanisms or about which patients with COPD are likely to benefit from intervention. As a result, there is little for the clinician to do but to treat all COPD patients similarly, despite their marked clinical heterogeneity.

COPD as an orphan disease would mean that pharmaceutical companies should reset their goals. Rather than a few blockbuster treatments, the goal should be many novel, but smaller, products. Interestingly, the approval of treatments for orphan subsets of the COPD population could help to reduce the costs of new treatments. The Orphan Drug Act makes treatments available based on safety and plausibility (*ie*, efficacy is not required as a criterion for approval). This should dramatically reduce both the cost and the time required for bringing a novel agent to clinical practice. In addition, further savings are possible. At the present time, in the United States, the major costs to a pharmaceutical company are not those for research and development, but those for marketing. Approval under an orphan indication may also help to reduce those costs. For example, for novel mechanistically based agents, prescription could be limited to those individuals who meet suitable diagnostic criteria, which would also form the basis for a data registry. With a narrowly defined therapeutic indication, promotional activities, and their costs, can be strictly limited. In addition, the treatment of a relatively homogeneous group of subjects is likely to result in a smaller number needed to treat in order to benefit a patient, reducing the costs to payers associated with patients who receive no benefit. Postmarketing data collection and marketing activities are subject to abuse by pharmaceutical companies. However, the regulation of these activities is within the purview of the FDA, which has the authority to enforce remedies to assure compliance.

As an orphan disease, COPD would become an attractive condition for relatively smaller companies rather than a condition restricted to large pharmaceutical companies with resources to compete in large markets. Large pharmaceutical companies also would benefit because these companies, with many promising compounds in their pipelines, would be more likely to promote the progress of more drugs to the marketplace.

Status as an orphan drug is granted by the FDA in response to a specific application that is made on the basis of the criteria noted above.[3] The role of the FDA is to be responsive. The proactive role must come from those developing novel treatments. The pharmaceutical industry, therefore, needs to embrace the concept of orphan drug development for COPD and should integrate this approach into all aspects of drug development from target definition, drug discovery, and product development. In particular, rather than seeking blockbuster treatments, this approach should foster a development program that can exploit the cost of development and marketing resulting in reduced costs for new therapeutic agents. Pharmaceutical companies have already shown an interest in viewing COPD as a group of disease subgroups rather than one large disease, with an example being the ongoing Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (or ECLIPSE) study.[18] Another way for pharmaceutical companies to embrace the concept would be to invest more in detailed patient characterization at baseline in controlled trials, enabling stratified analyses of these trials, either using the characteristics obtained or by reanalysis once a better understanding of biomarkers defining disease subgroups is achieved.

The classification of COPD as an orphan disease has some urgency. Understanding of the conditions that comprise COPD has advanced to the point where several dozen rational targets for therapeutic intervention have been identified, and compounds have been developed that potentially could impact these targets. However, in order to respond to exploit these opportunities, a revised view of COPD is required to define COPD subgroups, to develop relevant alternative biomarkers of disease progression, and to validate the targets already used for developing novel compounds. Without orphan status, it is unlikely that any of these goals can be achieved in a reasonable time frame. The reclassification of COPD as an orphan disease with a reorganization of the paradigms required for drug development together with a coordinated program of post-drug approval

surveillance and controlled marketing would be a major step forward in the campaign to address this disorder.

Summary

- Although COPD is extremely common, it should qualify for orphan status for two reasons: the condition is heterogeneous; and the various phenotypes of COPD likely represent specific conditions that are relatively rare.
- COPD progresses sufficiently slowly that it is unrealistic for a company to recover the costs of a drug designed to affect the natural history of the disease.
- The classification of COPD as a collection of orphan diseases could facilitate the development of more specific and more effective treatments.

This article has described the rationale and impact of reclassifying COPD as an orphan disease. Such a classification is realistic, both because COPD is a heterogeneous collection of syndromes that share a defining physiologic feature but differ in many respects, and because COPD progresses very slowly, making the cost of developing treatments to alter its natural history prohibitive. Drs. Vestbo and Rennard are pulmonary physicians with a long-standing interest in COPD. Both have participated in many clinical trials in COPD and have contributed to national and international guidelines. Dr. Vestbo's expertise is in epidemiology and Dr. Rennard's is in cell biology. The arguments applied to COPD in this article could be applied to many chronic, slowly progressive conditions that, based on advances in biological and clinical understanding, are now recognized as heterogeneous.

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