Hypothesis: in COPD, a pound of cure may be better than an ounce of prevention

Stephen I Rennard, Jorgen Vestbo

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the USA. Its defining feature is limitation of expiratory airflow, which is usually relentlessly progressive. Current therapies have meaningful, but limited benefits. For those who have resting hypoxaemia, supplemental oxygen improves survival. Rehabilitation can improve health status and exercise performance. However, neither of these treatments alters lung function or the rate at which it declines. Volume reduction surgery, by removing the most dysfunctional parts of the lung, can reduce exacerbations and improve lung function, performance, symptoms and survival, but only in a subset of patients, and the effects are limited, both in magnitude and in duration. Currently available pharmacotherapy, including bronchodilators and combinations of bronchodilators and inhaled corticosteroids, modestly improve airflow and symptoms and reduce exacerbations. Statistically significant effects in slowing the rate at which lung function is lost have been reported with pharmacotherapy, but the clinical importance of the benefits achieved remain uncertain.

With this background, a major goal for novel therapy in COPD is to alter the natural history of the disease. The classic study of Fletcher and colleagues provided the basis for current understanding of the natural history of COPD and has guided attempts at altering its course. The British Postal Worker’s Study included 792 men who were evaluated for a period of eight years. Based on this study, Fletcher and colleagues suggested that normal individuals lost lung function at an accelerating rate with age. Individuals who were exposed, for example, to cigarette smoke, and who were susceptible, experienced an accelerated rate of decline in lung function. A portion of these would eventually be diagnosed with COPD. To their credit, Fletcher and colleagues recognised that their ‘model’ was an extrapolation based on a limited data set and that only one parameter of COPD, airflow limitation, was considered.

The first large study designed to alter the course of COPD, and the only one that has demonstrated a positive effect testing the a priori hypothesis, was the ‘Lung Health Study’. This trial assessed smoking cessation, which was effective in slowing loss of lung function and the anticholinergic ipratropium, which was not. The sample size estimates were based on data from Fletcher and colleagues, as well as other studies, suggesting that COPD patients would be losing lung function measured as the FEV1 at an average rate of 60 ml/year in contrast to normal, which is closer to 20 ml/year. The study was powered with a target effect size of improving the COPD patients by half of the difference, that is to a 40 ml/year loss of FEV1. Two thousand subjects in three groups were studied over five years to demonstrate the benefit of smoking cessation in a post hoc analysis and the lack of effect of ipratropium in an intention to treat analysis. A subsequent follow-up at 11 years demonstrated the benefit of the smoking cessation intervention in the intention to treat group. The size and duration of the lung health study were a function of the slowly progressive loss of FEV1 in COPD. In order to have smaller and faster (and less expensive) clinical trials, many investigators have sought alternate measures. This has led to a new understanding of the complexity of COPD as well as to a number of alternate measures of the disease. However, the goal of all these efforts remains slowing the natural history of COPD, the goal sought by the Lung Health Study based on the model of Fletcher and colleagues. It may be paradoxical, but a much more ambitious goal, that is the cure of COPD, may be more easily achieved.

The large numbers of subjects and the long timeframes required when FEV1 is used as the measure of disease progression in COPD depend on the variance in the measure, which is well established at 55 ml, and the anticipated effect size, for which a goal of 20 ml/year improvement remains an elusive target. However, most diagnosed COPD patients have lost 50–70 per cent of the lung function present in young adulthood, a loss of perhaps 2000–2500 ml. Saving an additional 20 ml/year for the remainder of an individual’s life could be important, but is an extremely modest goal. In contrast, restoring even half of the lost function, for example 1000–1250 ml, would represent a much more robust treatment.

Therapy to cure COPD is not so far-fetched. A number of studies support the potential for such therapy. Retinoic acid, for example, can restore lung tissue in rodents with emphysema, though studies in man have been without clear benefit. Recognition that a selective retinoic acid receptor agonist may have greater effects offers a potential means to advance this line of therapy. Other agonists including hepatocyte growth factor and granulocyte colony stimulating factor may also have the capacity of stimulating alveolar wall formation following the development of emphysema. The latter is of particular interest, as recruitment of circulating stem/precursor cells may play a role. The ability of circulating cells to enter the lung, to become parenchymal cells and participate in repair, suggests a number of therapeutic strategies. For example, it may be possible to administer a stem/precursor cell population that can subsequently be stimulated with pharmacologic mediators. The availability of stem cells for clinical trials suggests that this type of strategy could be pursued in the near future. Lung repair can also be conceptualised for airways disease. In this context, airway fibrosis likely resembles fibrosis in other tissues, which, despite long held assumptions, may be reversible. In some settings, airways fibrosis does appear to resolve. In addition, the goblet cell metaplasia that is frequently present in patients with chronic bronchitis can reverse. Thus, strategies aimed at altering airway structure are also entirely feasible. Despite biological plausibility, therapy to restore lung function is generally regarded as a ‘pie in the sky’ type of goal. Paradoxically, it may be much easier to develop and more practical to implement.
in the clinical setting than the more modest goal of slowing disease progression. A therapy in severe COPD that would result in an effect size of 1000 ml in FEV1 would only require a handful of individuals in each group to have a 90 per cent chance of showing a benefit with a p<0.05. The timeframe would depend on the biology, but the ability of retinoic acid to stimulate alveolar wall formation in the animal model is easily detected in two weeks. Rapid effects discernable over short timeframes in small numbers of subjects would expedite dose ranging, and would thus simplify the need for biomarker intermediates and reduce the uncertainties inherent in the use of surrogates. Curative therapies, therefore, are likely to be developed over much shorter timeframes in smaller numbers of subjects and may have less risk of failure in phase III than treatments that slow disease progression. All these would reduce development costs.

Curative therapies are also likely to have advantages in clinical practice. Therapy designed to prevent disease progression is most effective when given in the presence of relatively mild disease. Serious adverse effects are not readily acceptable in this setting. In contrast, a curative therapy could be used exclusively in patients with very severe disease, in whom quality of life and survival are substantially compromised. This is particularly important for approaches that target mechanisms of cell proliferation and differentiation, which may have serious side effects, for example malignancy or fibrosis. For patients with very severe COPD, however, the potential risk of malignancy may be far outweighed by the reality of severe COPD.

Curative therapy is also likely to have fiscal advantages in clinical practice. Given the heterogeneity of COPD, it is likely that a ‘restorative’ therapy would be effective in a subset of COPD patients. A therapy designed to restore alveolar wall will only be of benefit in those with emphysema, for example. Thus, only a portion of the COPD population would be candidates for treatment. In addition, treatments may need to be given over relatively short timeframes. Thus, from a payor’s perspective, a curative therapy could have significant savings – due to the reduced number of treated patients and the reduction in long term visits and other supportive care. The net savings could accrue even if the medications were much more expensive than current drugs used to treat COPD.

The advantage of going for the cure in COPD has a clear analogy in cancer therapeutic strategies. Highly expensive therapy designed to eliminate, that is cure, cancer is generally regarded as cost effective and clinically relevant. A number of cancers have been successfully treated with this approach. In contrast, cancer prevention, short of eliminating risk factors such as cigarette smoking, has been strikingly unsuccessful. The lack of success in developing pharmacologic cancer prevention treatments stems from the same clinical limitations that have compromised the development of therapy to alter COPD’s natural history, that is, very large studies that require long timeframes. Without a doubt, the prevention of disease progression would be a wonderful clinical tool to have. However, it may be easier to develop treatments that cure the disease, and these should also be actively pursued.

Competing interests Stephen Rennard has served as a consultant or participated in advisory boards for: ABIM, Able Associates, Almirall Research, Almirall, APT, Aradigm, Argenta, AstraZeneca, BI (ACCP), Biostategies, BomCom, Britnall and Nicoleti, Capital Research, Chiesi, Clinical Advisors, CommonHealth, Complete Medical Group, Consult Complete, COPDForum, DataMonitor, Decision Resources, Defined Health, Day, Dunn Group, Eaton Associates, Enterprise Analysis, Equinox, Forest, Fullcrom, Gerson Lehmam, GSK, Guidepoint, Hoffman LaRoche, IMS, Informed, Inspire, Insyght, KOL Connection, Lierink Swan, M. Pankove, MDxR Medical, MedaCorp, Medimimum, Mpx, Novartis, Nycum, Ochel, Otsuka, Pearl, Pennside Partners, Pfizer, Pharma Ventures, Pharmaxis, Pick Research, Prescot, Pwc, Propagata, Pulmatix, Pulmonary Reviews, Quadrant, Reckner Associates, Recruiting Resource, Reviews and Trends in COPD/Convergent Health Solutions, Roche, Sacoor, Schering, Schlesinger Medical, Scimed, Smith Research, Sudler and Harressey, Talcis, Theravance, UBC, Uptake Medical, Vantage Point. He has received lecture fees from: AAAAA, Am Col Osteopathic Physicians, Asan Medical Center, ATS, AstraZeneca, California Soc Allergy, Convergent Health Solutions for Reviews and Trends in COPD, COPD Foundation, Creative Educational Concepts, Day, Duke Foundation, Information TV, University of California-Los Angeles, Network for Continuing Education, Novartis, Nycum, Otsuka, Pfizer, Sarasota Mem Hospital, Spanish Thoracic Society, University of Washington, University of Alabama-Birmingham, University of Pittsburgh, University of British Columbia, University of California-Davis, VA Sioux Falls. He has received industry-sponsored grants from: AstraZeneca, Biomarck, Cantocor, GlaxoSmithKline, Mpx, Nabi, Novartis, Otsuka, Pfizer. Jorgen Vestbo has received fees for consulting and presenting on issues on COPD treatment from the following pharmaceutical companies: GSK, AstraZeneca, Pfizer, Boehringer-Ingehelm, Novartis, Talcis, Chiesi, Hofmann-La Roche and Nycum — none of which provide a cure for COPD, unfortunately.

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