Interview

Chronic obstructive pulmonary disease: current & future directions

Dr Stephen Rennard is a Larson Professor of Internal Medicine at the University of Nebraska Medical Center (UNMC), NE, USA. Dr Rennard is widely recognized as a leader in the study of chronic obstructive pulmonary disease (COPD), the fourth leading cause of death in the USA. His groundbreaking research in the progression of lung disease has led to a better understanding of the disease and the development and testing of many new therapies. In 2006, he was selected as the first UNMC Scientist Laureate, the highest award given to a UNMC scientist, in recognition of his research in COPD, smoking cessation and lung-tissue repair and remodeling.

Stephen I Rennard
Larson Professor, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198, USA
Tel.: +1 402 559 7313
Fax: +1 402 559 4878
srennard@unmc.edu

■ What led you to focus your work on pulmonary diseases?

I did a BA in folklore and mythology, but I was always interested in science. I am very glad I did my BA as it was a wonderful opportunity to study a combination of literature and cultural anthropology, but I was never intending to be a full-time folklorist, and ultimately I chose medicine as my career. After medical school, I spent some time gaining research experience at the NIH, working on mechanisms of fibrosis in the lungs. Having done that for 2 years, I was interested in pursuing a research career and chose pulmonary medicine as my subspecialty, so that I could continue that work.

■ What are your main research interests?

I focus on chronic obstructive pulmonary disease (COPD), caused mostly, but not exclusively, by cigarette smoking. It is the fourth most common cause of death in the USA. The incidence is increasing, mostly due to the past epidemic of smoking, but approximately 20% of COPD patients are lifelong nonsmokers, so it would be a major public health problem even in the absence of smoking. It includes several entities such as emphysema and bronchitis, and also has extrapulmonary manifestations. We study both the basic mechanisms of the disease, especially as it relates to alterations in tissue structure, with the intent of being able to reverse those changes, and are involved in clinical studies looking at the mechanisms that underlie the disease and the development of novel therapies.

■ How much has our understanding of the mechanisms of chronic obstructive pulmonary disease improved during the time you have been in the field?

There have been some fairly significant advances. You can always ask more questions about the way things work, but we now know that inflammation plays a major role in the development of COPD, and we have identified some of the pathways by which inflammation causes those changes in the lungs. We also know that there is considerable person-to-person heterogeneity in the response to lung injury, such as that caused by cigarette smoke, which depends on complex genetic factors, not all of which are well understood. We also understand something about how the tissues come to be altered, enough to speculate on possible strategies to make the tissue better.

To date, advances in therapy for COPD have been very modest. There have been some, but much less than we would like. A lot of the potential for these advances in our understanding to improve therapies still remains to be realized.

As the understanding of the disease has advanced, some of the ways in which we clinically approach the disease need to be expanded. We are still approaching the disease in the same way we would have done 40–50 years ago, and that may not be the best strategy for developing therapies based on newer concepts. Some clinical advances need to take place to keep pace with the mechanistic advances.

future medicine part of fsg

■ Smoking is the major risk factor for COPD. Looking at your work on smoking cessation, what are the key factors that lead to successful smoking cessation?

People tend to underestimate the problem of smoking. It should be regarded as a disease. The vast majority of people who smoke are addicted, and even when you give up you are not necessarily a lifelong nonsmoker. A lot of people are at risk of relapse, so in some ways the model is similar to a cancer patient in remission. Smoking is a very complex behavior. There is clearly an addictive component, but there is also a behavioral component. Usually people are smoking multiple times in a day for many years: it becomes integrated into their lifestyle. People need to deal with both addictive and behavioral aspects to quit. There is very good evidence that nonpharmacological support can help people quit, and this is improved if supplemented with pharmacological treatment.

■ What factors other than smoking increase the risk of COPD?

Tobacco smoking is far and away the most important risk factor. Some of the nonsmokers may also have passive smoke exposure. However, smoking is not the only cause: air pollution can contribute; it is likely that asthma can progress to COPD; and genetics can have an impact. There is one genetic risk factor that is very well established, α1-antitrypsin, a blood protein. If this factor is deficient, people are at risk of COPD whether they smoke or not, and if they do smoke they are at much greater risk.

Indoor air pollution is a major problem, not so much in the USA, but particularly in developing world countries where biomass fuels are used, and women develop chronic bronchitis, a form of COPD, at a high frequency, presumably due to exposure to fumes generated by biomass fuels.

■ What is the role of genetic versus environmental factors in COPD?

It is very hard to answer that question accurately. There is tremendous interplay between environmental and genetic factors. You could say that the percentage that is genetic is 100% and the percentage that is environmental is 100%. People say that only a minority of smokers will suffer from COPD, but that is not correct. Maybe a minority get sufficiently severe COPD that they come to diagnosis, but COPD is vastly underdiagnosed. The majority of smokers who smoke long enough will get COPD: they may not come to diagnosis, but current evidence suggests that even if they have not yet been diagnosed they probably have limited lung function and have increased morbidity as a consequence. That said, there is clearly variable susceptibility: some people can smoke a lot and are relatively unaffected, and others who are nonsmokers suffer from severe disease.

■ Do you see COPD therapy becoming more personalized to individual patients?

I think that all therapies will be more personalized in the future: that is certainly the goal. COPD is very heterogeneous. At the moment most therapies are one-size-fits-all, but that is not conceptually appealing. To give an example, there are some therapies that can reduce the risk for acute exacerbations, but not all COPD patients have exacerbations, so obviously those medications are of little use to them. We would like to have therapies that are more specific for slowing the rate at which the disease progresses. It is likely that people have progressive disease for a variety of reasons, so you would need to identify the reasons behind why a patient is progressing, and develop therapies that are specific to the cause.

■ Given the negative results of the 2007 clinical trial of infliximab therapy, what is the role for antibody therapies in COPD?

The 2007 study was testing whether anti-TNF antibodies would be effective in an unselected group of patients with COPD, and that was negative [1]; however, that does not answer the question of whether it could work in a subset of patients or at a specific time in the disease process. Of course, studies looking at antibody therapies against other targets have been carried out or are in progress, so I think we will hear more in the future about antibody therapies targeting specific mediators in COPD.

■ What do you see as the future of COPD therapy?

There are three major classes of drugs available (not including oxygen), and we can expect to see new drugs in all three of these (β2-agonists, anticholinergics and corticosteroids), as well as new combinations of drugs, which will be advantageous for patients. There has not been a new class of drugs for COPD for a number of years. However, a type of phosphodiesterase (PDE)-4 inhibitor has just been submitted for US FDA approval, so that is likely to be the next new class of drugs in COPD. The concept is that PDE-4 inhibitors will decrease the inflammation that we think plays an important role in COPD, whereas the other drugs are primarily directed towards causing smooth-muscle relaxation and are functioning as bronchodilators.

I am very optimistic for the future of COPD. There have been a lot of mechanisms that hold great promise. The clinical approach to the disease needs to catch up, but several studies are ongoing or will be started shortly that should further advance our clinical understanding of COPD. There are at least two large-scale studies, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), funded by GlaxoSmithKline (London, UK), and SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS), funded by the NIH, that should provide an extraordinarily rich set of information to help subcategorize patients with COPD and advance their clinical assessment for the purposes of developing and implementing novel therapies.

There are a lot of reasons why we should be enthusiastic about the future. There are several therapies currently being assessed, with a list of more than 60 novel drugs in development. A decade from now I suspect that the clinical approach to COPD will be dramatically different from today.

Financial & competing interests disclosure

Prof. Rennard has had or currently has a number of relationships with companies who provide products and/or services relevant to outpatient management of chronic obstructive pulmonary disease. These relationships include serving as a consultant, advising regarding clinical trials, speaking at continuing medical education programs and performing funded research both at basic and clinical levels. The author does not own any stock in any pharmaceutical companies.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1 Rennard SI, Fogarty C, Kelsen S *et al.*: The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 175(9), 926–934 (2007).