A new chapter in therapy for cystic fibrosis

In the New England Journal of Medicine, Wainwright and colleagues reported the results of two phase 3 studies to assess the effects of a combination of lumacaftor and ivacaftor for the treatment of cystic fibrosis; specifically, in patients homozygous for the most common mutation in the gene encoding the cystic fibrosis transmembrane regulator (CFTR) protein, Phe508del. Although cystic fibrosis is a single-gene disease, wherein mutations in CFTR cause abnormalities in protein function and thus chloride-channel activity in the lungs and other secretory organs, more than 1000 mutations in CFTR have been identified, and the task of finding therapies appropriate for each mutation might seem too difficult a task (although not all of these mutations cause disease). However, recognition of the class effect of specific mutations at different points in the gene, ably described by Boyle and De Boeck in a Review in The Lancet Respiratory Medicine, has also allowed the design of classes of drugs that have specific effects on different mutation classes. The lumacaftor–ivacaftor combination is based on that approach and the results of these trials bring hope of mutation-specific therapy to more patients with cystic fibrosis.

Ivacaftor was licensed in Europe and the USA for the treatment of cystic fibrosis in patients with the Gly551Asp (class 3) mutation, in whom dysfunctional CFTR is present in the cell membrane. Ivacaftor is a CFTR potentiator, which ensures that the CFTR functions appropriately and stays open to allow chloride flux. Oral ivacaftor given twice per day was associated with improvements in lung function and other outcomes in a clinical trial, but this treatment is only suitable for the 5% of patients with cystic fibrosis who have the Gly551Asp mutation. The effectiveness of the lumacaftor–ivacaftor combination brings hope of therapy to more patients with cystic fibrosis—more than 50% of people with cystic fibrosis in the UK are homozygous for the Phe508del mutation.

Although evidence of a significant effect of the lumacaftor–ivacaftor combination is exciting, some caveats must be considered. First, compared with the results from the ivacaftor study in patients with the Gly551Asp mutation, the changes in lung function from baseline in the lumacaftor–ivacaftor trials are not so impressive—ie, from 2·6 to 4·0 percentage points in predicted forced expiratory volume in 1 s—although, encouragingly, the combination therapy did seem to be associated with a reduction in pulmonary exacerbations. Second, 17 (4·6%) of 369 patients who received the higher dose of lumacaftor treatment discontinued because of adverse events, compared to six (1·6%) of 370 patients who received placebo, a difference not seen in the ivacaftor monotherapy trial, in which only one (1%) of 83 patients receiving ivacaftor discontinued because of an adverse event, compared with four (5%) of 78 patients who received placebo.

Does the combination of lumacaftor and ivacaftor represent the future for patients with Phe508del homozygous cystic fibrosis? Wainwright and colleagues’ results suggest that drug–drug interactions between ivacaftor and lumacaftor could cause problems for some patients and an optimum dose regimen might not have yet been identified. Furthermore, alternative drugs to lumacaftor (the corrector agent in the combination that ensures the abnormal protein reaches the membrane) might be identified that work better in combination with ivacaftor.

The publication of these trial results have brought excitement and hope for the future, but this reaction should be tempered by concerns regarding the future funding of cystic fibrosis care. Health systems, including the UK National Health Service, have been burdened by the high cost of ivacaftor, which has so far benefited only a small proportion of patients. Negotiations should be pursued to ensure that a realistic price is set internationally for the lumacaftor–ivacaftor combination, especially because so many patients with cystic fibrosis are potentially eligible for the treatment and because the weaker effect seen with the combination compared with ivacaftor monotherapy should result in a lower price. Following the hard work put in by drug developers and trial collaborators, cystic fibrosis physicians worldwide should work together to define a threshold of clinical change that makes such expensive mutation-specific therapies cost-effective.

I was a subinvestigator on the lumacaftor and ivacaftor trials.

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COPD management: need for more consensus

I would like to applaud Christopher Cooper and Igor Barjaktarevic for their new algorithm for the management of chronic obstructive pulmonary disease (COPD). They fill the gap left by the Global Initiative