P38 inhibition in COPD; cautious optimism

Dave Singh

The nature of inflammation varies greatly between COPD patients, leading to heterogeneity in clinical manifestations. For example, emphysema is severe in some patients but minimal in others. The varied nature of COPD inflammation means that a novel anti-inflammatory drug is unlikely to be effective in all patients. This is certainly true for established anti-inflammatory therapies such as inhaled corticosteroids, which are most effective in the subgroup of patients with a history of exacerbations, and also those with evidence of increased sputum eosinophils. The PDE4 inhibitor, rolflumilast, also shows greater efficacy in a COPD subgroup; those with chronic bronchitis and a history of exacerbations.

The p38 mitogen activated protein kinase (MAPK) signalling pathway promotes inflammation by enhancing inflammatory gene transcription, stabilising mRNAs and increasing protein translation. p38 MAPK signalling is activated by different extracellular stimuli that are relevant to COPD, such as cytokines, toll-like receptor agonists and oxidative stress including components of cigarette smoke. Furthermore, lung immunohistochemistry studies have demonstrated increased p38 MAPK activation in COPD patients compared with healthy controls. p38 MAPK inhibitors reduce cytokine production from different COPD lung cells in vitro, including alveolar macrophages, lymphocytes and bronchial epithelial cells. These observations from laboratory studies indicate that p38 MAPK activation contributes to COPD inflammation, and have encouraged the development of p38 MAPK inhibitors to treat COPD.

Orally administered p38 MAPK inhibitors have been developed for the treatment of inflammatory diseases including rheumatoid arthritis. Unfortunately, these drugs have caused unacceptable side effects including liver toxicity and skin reactions. Additionally, the efficacy appears to be transient; initial improvements in systemic inflammatory biomarkers including C-reactive protein (CRP) disappear within weeks. This may be due to ‘redundancy’, where blocking one pathway within a complex inflammation network simply diverts the signal to activate a different pathway. p38 MAPK inhibition may result in upstream kinases redirecting signalling through other MAPKs, such as extracellular signal-related kinase (ERK), and c-Jun N-terminal kinase (JNK) to propagate inflammation. We hope that the transient efficacy observed in rheumatoid arthritis patients does not occur in COPD clinical trials of p38 MAPK inhibitors. The mechanisms of inflammation differ between these two diseases, and activation of redundant MAPKs after p38 MAPK inhibition may not occur in COPD. Nevertheless, treating inflammatory diseases using highly selective p38 MAPK inhibitors may be an approach that is too focused; using drugs that also target a wider spectrum of inflammatory kinases may overcome redundancy. Furthermore, most p38 MAPK inhibitors, including the novel inhibitor PH-797804, selectively target the α isof orm which is highly expressed on immune cells. However, the other isof orms (β, γ and δ) may also be important in inflammation, and certainly are expressed in COPD lung tissue.

Broader targeting of p38 MAPK isof orms may be more effective in COPD. Macnee et al report a 6-week parallel group, placebo controlled, randomised clinical trial in COPD patients of the orally administered p38 MAPK inhibitor PH-797804. The dose-response effects of 0.5, 3, 6 and 10 mg once daily were evaluated, with more patients receiving 6 mg, as this dose was anticipated to have the optimum therapeutic index. An interim futility analysis resulted in no further patients being recruited to receive the 0.5 mg dose as there was <10% chance of achieving ≥75 ml improvement over placebo in FEV1 change from baseline. The final randomisation included more patients who received 6 mg (n=70), compared with the remaining treatment arms (n=45 to 48). The 6 mg dose had the greatest clinical efficacy, demonstrating a statistically significant 93 ml improvement in FEV1 compared with placebo associated with an improvement in breathlessness measured using the TDI (0.99, p=0.049), and also significant improvements in inspiratory capacity and rescue medication use. The lung function improvements coupled with symptomatic benefits is convincing evidence of a therapeutic effect. However, this study had a limited sample size, and there were wide 95% CIs from 18 to 166 ml for the FEV1 change caused by PH-797804 6 mg compared with placebo. The true effect of this drug will only become apparent in larger studies. PH-797804 treatment was associated with some side effects, notably a rash, but was generally well tolerated.

The effects of PH-797804 3 mg and 10 mg were smaller than the 6 mg dose. PH-797804 10 mg caused a non-significant 66 ml improvement in FEV1 compared with placebo, while the TDI score and rescue medication use were also not different to placebo. The reason for the apparent effectiveness of 6 mg but not 10 mg is unclear. Let us speculate. In rheumatoid arthritis, p38 MAPK inhibition may lose effectiveness due to redundant mechanisms; it is possible that the degree of p38 MAPK inhibition caused by the highest PH-797804 dose activated other MAPKs that consequently negated any therapeutic effect? A counter argument is that doses from 3 to 10 mg suppressed CRP levels at 6 weeks, indicating no loss of effect of the 10 mg dose in the systemic circulation. A different reason for this result could be that a smaller sample size received 10 mg compared with 6 mg, reducing the statistical power to detect drug effects at the higher dose. Nevertheless, this study has reported an apparently bell-shaped dose response curve, and understanding the reason for this may be very important for advancing our understanding of the p38 MAPK pathway in COPD.

The patients recruited for this study of PH-797804 were not restricted to a particular phenotype, but were simply moderate to severe COPD patients. PH-797804 might be most effective in a subgroup of COPD patients with inflammation that is highly dependent on P38 MAPK activation. Do we have any clues as to the clinical characteristics of this phenotype? The oral p38 MAPK inhibitor losmapimod did not change FEV1 over 12 weeks in COPD patients, but a cluster analysis showed an improvement in hyperinflation measurements. PH-797804 also improved inspiratory capacity. p38 MAPK activation is increased in the small airways of COPD patients, so perhaps p38 MAPK inhibitors reduce small airway inflammation, thereby reducing air trapping in patients with hyperinflation. Alternatively,
it has been reported that quadriceps inflammation in COPD patients is associated with increased p38 MAPK activation, although another study failed to replicate this finding. PH-797804 and losmapimod both reduced systemic biomarkers of inflammation in COPD patients, suggesting that these drugs have systemic activity which may target p38 MAPK-driven muscle inflammation.

Losmapimod failed to show an effect on the primary endpoint of sputum neutrophils in COPD patients. The effects of PH-797804 on airway inflammation were not measured. Measuring in neutrophils in COPD patients. The effects of PH-797804 on airway inflammation were not measured.16 Measuring inflammation in COPD clinical trials can be difficult, as sputum studies can be prone to practical difficulties and variability, while bronchoscopy studies are invasive. One assumes that the improvement in FEV1 caused by PH-797804 was due to an anti-inflammatory effect on lung cells. However, oral p38 MAPK inhibitors may also exert therapeutic benefits by targeting systemic inflammation in COPD patients, and the extent to which these drugs inhibit pulmonary inflammation is currently unknown. Oral p38 MAPK inhibitors often have systemic side effects, and a possible future avenue for development of novel anti-inflammatory drugs for COPD has been notoriously difficult, as it is necessary to understand the likely ‘responder’ populations. The clinical phenotype most likely to respond to PH-797804 is currently unknown, and needs to be defined for the drug to stand the best chance of being successfully developed. There are other important questions about PH-797804 that also need answering; how well will it work when given with inhaled corticosteroids? Will the side-effect profile be acceptable? Rheumatologists have grown pessimistic about the potential of p38 MAPK inhibitors. We can be cautiously optimistic about PH-797804 in COPD, but there are still considerable challenges ahead.

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