NEW DRUGS AND TARGETS FOR COPD

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The mainstay of current drug therapy for COPD is long-acting bronchodilators. Several once a day inhaled β_2-agonists (LABA) are in development for COPD and indacaterol is already launched in some countries. Once daily included muscarinic antagonists (LAMA) in addition to tiotropium are also in clinical benefit and combination inhalers containing a LABA and LAMA look very promising.

COPD is corticosteroid-resistant so alternative anti-inflammatory approaches are in development. Understanding the cellular and molecular mechanisms of COPD will lead to new approaches to therapy in the future, and in particular to drugs that will prevent disease progression, reduce mortality and treat the multiple systemic effects and comorbidities of COPD. Many mediators are involved in COPD, so blocking individual mediators may not be very effective. Blocking cytokines has so far been unsuccessful, but new drugs that block the receptor for neutrophil chemokines (CXCR2) are more promising. The lung destruction in COPD is due to release of proteases, including neutrophil elastase, suggesting that enzyme inhibitors might be effective. There is particular interest in matrix metalloproteinases (especially MMP-9) that are released from macrophages and neutrophils and selective MMP inhibitors are in development. Oxidative stress may be very important in COPD in amplifying inflammation, increasing proteolysis and induction of steroid resistance. More effective antioxidants are needed in the future. Phosphodiesterase(PDE4)4 inhibitors may be effective in neutrophilic inflammation, in contrast to corticosteroids and roflumilast has recently been launched. This drug has a small effect on lung function and reducing exacerbations but its benefit is limited by dose-related side effects. Other anti-inflammatory approaches include nuclear factor-κB, p38 MAP kinase and phosphoinositide-3 kinase(PI3K)-γ inhibitors, which are in the early stages of clinical development.

Theophylline appears to have a unique action of stimulating histone deacetylase (HDAC) activity and thereby reversing steroid-resistance induced oxidative stress. This mechanism is via inhibition of PI3K-δ and selective inhibitors are now in clinical development. Macrolides (antibiotic and non-antibiotic) are also able to reverse corticosteroid resistance and this might be a more effective and safer approach than developing new anti-inflammatory treatments that are likely to be limited by side effects.

It is likely that both bronchodilators and anti-inflammatory treatments will need to be given by inhalation in order to reduce systemic toxicity. More attention needs to be given to delivering the drugs to the peripheral airways and lung parenchyma, particularly in the presence of heterogeneous airway obstruction