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The COPD Pipeline, XXX

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Abbreviations: phosphodiesterase inhibitor, **PDEi**; chronic obstructive pulmonary disease, **COPD**; alpha-1 antitrypsin, **AAT**
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Phosphodiesterase Inhibitors

Roflumilast was the first phosphodiesterase inhibitor (PDEi) other than theophylline to be approved for chronic obstructive pulmonary disease (COPD). However, its propensity to produce undesirable side effects, principally gastro-intestinal ones, has hampered its widespread use. But that agent has anti-inflammatory actions, at least *in vitro*, as well as its Food and Drug Administration- approved indication to reduce the frequency of acute exacerbations of COPD. Roflumilast provided proof of concept for the development of several other PDE's for COPD. Several pharmaceutical companies have targeted COPD with novel phosphodiesterase inhibitors to meet the large and unmet needs of COPD patients. The well-known PDE5 inhibitors, sildenafil, tadalafil and udenafil, appear to have little or no beneficial action on the airways of COPD patients.[1,2] But several novel PDE4 antagonists are in development. They are discussed below.

RPL554

RPL554 is an interesting example. Verona Pharm's lead product is a phosphodiesterase inhibitor that inhibits both PDE3 and PDE4. It is being developed for asthma and cystic fibrosis as well as COPD.[3,4] The drug is novel both in that it can be delivered by inhalation and it inhibits 2 relevant phosphodiesterase inhibitors. The PDE3 component relaxes airway smooth muscle, and the PDE4 component inhibits the activation and release of inflammatory mediators. RPL554 has been effective and well tolerated in one small proof-of-concept study[5] and is now entering a Phase II trial (NCT02542254). In a six-arm crossover study, 30 individuals with COPD will receive placebo or short-acting albuterol or ipratropium or combinations of these in addition to a single dose of RPL554.[6]

Tetomilast

Otsuka Pharmaceutical Company will initiate 2 randomized controlled double blind trials of its oral PDE4i tetomilast. A total 771 individuals will be enrolled in the 24 month Phase II trials.[7]

CHF6001

CHF6001 is Chiesi Farmaceutici's novel PDE4i that is being developed for inhalational use.[8] *In vitro* studies show it to be a highly selective inhibitor of PDE4's in general although not selective for specific PDE4 subtypes. It is also potent as compared to roflumilast and some other PDE4i's. Its anti-inflammatory activity is described as robust and suitable for topical pulmonary administration, a novel device, NEXThaler, is used for delivery. There have been 4 completed early phase trials, none of which has yielded published results. An ascending dose trial is in progress (NCT02386761).[9]

GSK256066

GSK256066 is described as a high-affinity and selective

inhibitor of PDE4 with equal affinity for each of the 4 PDE4 isoforms.[10] Its potency is at least as great as that of other PDE4i's. When delivered intra-tracheally to rodents it inhibited induced pulmonary neutrophilia with greater potency than fluticasone. One Phase II study of GSK256066 for COPD, a randomized, double-blind, placebo controlled study in 104 patients has been completed (NCT 00549679), and published.[11] The drug was delivered by inhalation and was well accepted without an increase in gastro-intestinal disturbances. Lung function was marginally improved. The drug is also in 8 studies for asthma, allergic rhinitis, and endotoxin induced airways inflammation.

Apremilast

Apremilast, a PDE4 inhibitor from Celgene, is being developed for a number of other inflammatory conditions including possibly COPD,[3] (but if so, has not registered for that indication in clinicaltrials.gov. Similarly, Asubio has a PDE4/7 inhibitor in development that might be of interest in COPD,[3] but it is also not yet registered in clinicaltrials.gov.

Other Drug News

Glassia

A clinical trial by Kamada, Ltd. (NCT02614872) will undertake a randomized open-label Phase II study of 30 alpha-1 antitrypsin (AAT) deficient individuals undergoing lung transplantation.[12] Half of the individuals will receive Kamada's AAT Glassia in addition to usual care. The remainder will receive usual care. The primary outcome will be the percentage of individuals experiencing any treatment-emergent serious and/or non-serious adverse events regardless of causality.

Mepolizumab

Mepolizumab is a monoclonal antibody that inhibits IL-5. It was approved by the Food and Drug Administration in November 2015 for the maintenance treatment of severe asthma that has an eosinophilic phenotype when patients are not well controlled despite usual asthma therapy.[13] Its brand name is Nucala. It has been known for some years that in patients with COPD the frequency of acute exacerbations of COPD may also be reduced by mepolizumab.[14] In the cited publication, the frequency of hospitalizations for acute exacerbations of COPD was reduced approximately 50%. Other studies estimate that 20% of COPD patients with asthma may have an eosinophilic component to their airway disease.[15] Consequently, clinical trials with mepolizumab for COPD are in progress. The developer, GlaxoSmithKline, has 2 similar multicenter Phase III studies of the drug in progress (NCT02105948 and NCT02105961).[16,17] The drug will be administered as an add-on to usual therapy and the primary outcome is the frequency of acute exacerbations. A smaller study from McMaster University with sputum eosinophil counts as the endpoint has recently been completed (NCT01463644).[18] The agent is administered by injection on a monthly basis. Adverse events include headache and local injection reactions.

Reslizumab

Concerns about the safety of a different anti-IL5 biologic, reslizumab (Teva), have been raised and were discussed at a Food and Drug Administration Advisory Committee meeting last December. Their comments are not available at the time of writing. Five cases of anaphylaxis and some cases of muscle disorders were reported in the Phase III studies.

Tacholiquine

Tacholiquine is a preparation containing tyloxapol, a surface-active ingredient. Tacholiquin (sic) has been available as an inhaled mucolytic agent for several decades. A randomized, double-blind, placebo controlled Phase IV trial (NCT02515799) has just been completed.[19] It involved 27 COPD patients over 3 weeks; the primary endpoint was sputum weight. No results are available as yet.

AZD5069

AZD5069 is a small molecule CXCR2 inhibitor. CXC is predominantly expressed on neutrophils and mediates the migration of neutrophils to inflammatory sites. It is considered to be an appropriate target for inflammation. In 2 recently published controlled trials, AD5069 was administered orally to healthy volunteers[20] and patients with moderate to severe COPD.[21] The agent was "well tolerated" by the patients and will, presumably, proceed to further COPD studies. The agent is also in early phase trials for asthma and some malignancies.

Neutrophil Imaging in COPD

Clinical trial NCT02551614 is an "exploratory study to develop an imaging platform for the assessment

of whole lung neutrophil retention."[22] The primary objective of the study is to quantify and compare neutrophil retention in the lungs of lipopolysaccharide-challenged healthy individuals, or saline-challenged healthy individuals and individuals with stable COPD. The Phase I study will consist of 1 week with the primary outcome being the uptake of labelled neutrophils in the lung as assessed by single-photon emission tomography (SPECT).

A Universal Influenza Vaccine?

Broadly neutralizing human antibodies which target the highly conserved hemagglutinin stem of the influenza virus have recently been identified. This raises the possibility that a universally protective influenza vaccine may be feasible. A recent report discusses this concept.[23]

New Developments in Inhaler Devices

The number of inhaler devices has increased substantially in recent years but little research has shown whether the clinical outcomes of their use have improved. A recent review of 30 trials that compared inhaler devices showed that "the only well-documented effect was found for the Respimat® Soft Mist™ Inhaler, which achieves a more than 3-fold lowering of the once-daily tiotropium dose through increased performance of the inhaler device." Otherwise, "new inhaler devices may improve patient satisfaction but do not lead to demonstrable improvements in clinical efficacy."[24]

Chiesi's Fixed Triple

Chiesi's fixed triple consisting of budesonide/formoterol/glycopyrronium (200/12/25mcg) twice daily will be compared to Ultibro®, the fixed combination of indacaterol/glycopyrronium (85/43mcg) once daily (NCT02579850).[25] A total of 1534 patients with severe or very severe COPD will be recruited to a 1 year study, the primary outcome being the rate of moderate to severe acute exacerbations of COPD.

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