Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

The COPD Pipeline, XXVIII

Nicholas Gross, MD, PhD[1,2]

Abbreviations: long-acting muscarinic antagoinist, **LAMA**; forced expiratory volume in 1 second, **FEV_1**; long-acting beta-agonists, **LABA**; Food and Drug Administration, **FDA**; GlaxoSmithKline, **GSK**; muscarinic antagonist-beta2 agonists, **MABA**; inhaled corticosteroids, **ICS**; phosphoinositide 3 kinase, **PI3K**; asthma COPD overlap syndrome, **ACOS**; cellular and gene therapy, **CGT**; poly-lactic-co-glycolide acid, **PLGA**; Pharmaceutical Research and Manufacturers of America, **PhRMA**; computed tomography, **CT**

Funding Support: n/a
Citation: Gross N. The COPD Pipeline XXVIII. *J COPD F.* 2015; 2(3): 259-263. doi: http://dx.doi.org/10.15326/jcopdf.2.3.2015.0149

1 Stritch-Loyola School of Medicine, Chicago, Illinois

2 St. Francis Hospital, Hartford, Connecticut

Address correspondence to:

Nicholas Gross, MD, PhD
grossnicholas1@gmail.com

Keywords:

devices; OL-BF-001; TD-4208, SUN-101; porous particles, danirixin; ACOS; low-dose theophylline; JBT-101; resumab; QBW251; aspirin

Endobronchial Devices

Studies of endobronchial devices continue in the United States with phase III trials ongoing for the Spiration valve[1] and the Pulmonx Zephyr valve[2] that depend on intact inter-lobar fissures and heterogeneous emphysema. The Lung Volume Reduction Coil Treatment in Patients with Emphysema: RENEW study,[3] using endobronchial coils for heterogeneous and homogeneous emphysema regardless of fissure integrity, has completed enrollment with results expected the first quarter of 2016. All of these devices are approved in Europe where they are occasionally mixed and matched for unique clinical situations. Phase III trials are also ongoing outside the United States with the Uptake Medical system[4] that uses a carefully measured dose of steam to injure airways serving emphysematous lung regions. With healing and reduction in lung volume distal to the injury site, patients may receive benefit without a foreign body in the airway. Since the valves are removable, they are often used first in patients with complete fissures. There are no randomized head-to-head trials between different devices.

Importantly, these are licensed (only in Europe) for individuals with emphysema and significant hyperinflation and probably do not work for other phenotypes of COPD.

OL-BF-001

Within endobronchial devices, there is a new umbrella-type device, the OL-BF-001. According to the sponsors, Olympus Corporation, "OL-BF-001 consists of a bronchial valve, deployment catheter, loader and airway sizing kit."[5] Trial participants will have severe COPD and the primary outcome will be the responder rate as determined by the St. George's Respiratory Questionaire (NCT02470052). The trial has yet to begin.

Long-acting Muscarinic Antagonists

TD-4208

A long-acting muscarinic antagoinist (LAMA), TD-4208 is being developed by Theravance as a nebulized 24+ hour bronchodilator for COPD. The molecule is structurally quite different from most other quaternary ammonium bronchodilators. It is as selective for M3 receptors as tiotropium, has potency that is equivalent to tiotropium *in vitro*, while being less selective than tiotropium for salivary glands in animal studies, presumably producing less of a dry-mouth. Four trials are registered in clinicaltrials.gov. A phase IIb dose-ranging study met the primary efficacy endpoint (trough forced expiratory volume in 1 second [FEV_1] following the last dose on day 28) with statistically significant responses at once-daily doses of 88 mcg and above. Onset of meaningful bronchodilation was between 30 and 60

minutes. A striking, and I believe unique, finding was that the elevation in FEV_1 persisted almost unchanged throughout the 24 hours of observation. This suggests, to me at least, that its bronchodilator action exceeds 24 hours. The safety outcome was good.[6]

The latest trial of TD-4208, a phase III, 12 week trial, is due to start enrollment at time of writing (NCT02459080). It is a randomized, placebo-controlled, double-blind, 3-armed trial, employing 2 doses of the drug and a placebo arm. The number of participants is not given and the primary outcome is *pulmonary function test*. Mylan Pharmaceuticals also has an interest in this agent. Mylan already has the 12-hr nebulized LABA formoterol, Perforomist™, and in a press report, states they may use TD-4208 to develop a fixed long-acting beta-agonist (LABA)-LAMA nebulized product.[7] It could be the first such nebulized combination for COPD. One wonders how the fixed combination of a 12-hour LABA and a 24+ hour LAMA will be viewed by the Food and Drug Administration (FDA).

SUN-101

Sunovion is also working to develop a nebulized LAMA, glycopyrrolate, SUN-101, delivered by the Pari eFlow® device. A 48- week head-to-head trial with tiotropium is underway (NCT02276222).

GlaxoSmithKline's Respiratory Pipeline

The GlaxoSmithKline (GSK) respiratory pipeline is quite deep and broad. They have 2 phosphoinositide 3 kinase (PI3K) inhibitors, one for idiopathic pulmonary fibrosis in phase I and another for asthma and/or COPD in phase II. They have 2 LAMA-LABA agents in early stages, despite obtaining FDA approval for anoro last year. I believe they have at least 2 *triples* one of which is a muscarinic antagonist-beta2 agonists (MABA)/ inhaled corticosterdois (ICS) in phase II. Their anti- IL-5 monoclonal antibody mepolizumab is in 2 trials, one of which is in phase III for COPD. Their oral p38 kinase inhibitor losmapimod is in phase II for COPD. Danirixin, a CXGR2 chemokine receptor antagonist, is in phase II aimed at the asthma COPD overlap syndrome (ACOS) (see below). They also have a soluble epoxide hydrolase inhibitor in phase I for a COPD indication. In all, for COPD they have 2 products in phase I, 5 in phase II and 4 in phase III. Besides these, GSK also has novel agents for other lung conditions. Their full respiratory pipeline as of earlier this year can be found at on their website.[8]

Theravance also has a MABA, GSK961081 that is now being developed by GSK. Eight trials have been completed, the latest, a phase II trial is NCT00674817.

The FDA's Cellular and Gene Therapy Advisory

We are moving into the phase of cellular and gene therapy (CGT) when unexpected things can happen. The FDA has advised as follows: "Because cellular and gene therapy products can have more severe effects than other types of drug products, potentially leading to organ failure, tumors or death, sponsors should include these as primary safety objectives when designing early-phase clinical trials."[9]

The trial should assess the nature and frequency of potential adverse events and how they relate to dose, the final guidance says. A year or more of follow-up is appropriate for each individual. For CGT products that remain active in the body indefinitely or where there is concern that cells might transform, migrate or cause ectopic tissue to develop, monitoring should continue for many years, the FDA advises.[9]

Porous Particles

Although treatment of lung disorders is greatly facilitated by inhalation because it provides direct access of drugs to the target, the current pharmacokinetics of an inhaled drug are seen as less than ideal. The peak action of an inhaled agent occurs relatively early and is followed by a steady decline throughout the rest of its action. This creates the potential for adverse events during the period when the drug and its effect are at peak, and a prolonged decline in its effect towards baseline. In the era of long-acting drugs for maintenance use these problems are greatest. Industry is looking for ways to "even out" the release and action of the drugs we wish to administer by nebulization. Attempts are being made to develop carriers to which a drug may be attached that will release the drug in a sustained and steady rate over long periods of time.[10] Among many potential carrier agents, poly-lactic-co-glycolide acid (PLGA) is seen as a potential microcarrier for both respiratory and non-respiratory drugs.[11] As a polymer, its molecular weight can be increased or decreased in a manner that permits tuning the rate of release of an attached agent. However,

if used over the long term, concerns can be raised about the safety of accumulated PLGA and its degradation products in the lungs.

Almost 2 decades ago, the suggestion was made that porous particles could be used to carry drugs absorbed on their surface for delivery into the lungs and to release the drugs at a controlled rate.[12] If made large enough, the particles would avoid alveolar phagocytosis, but have low enough bulk density to nevertheless reach the distal lung. Among the numerous agents that have been explored for delivery by PLGA carriers are insulin, LMW heparin, budesonide, methotrexate, and ciprofloxacin. Other drug delivery systems for controlled pulmonary release include a variety of microparticles, liposomes, and swellable microparticles. The pros and cons of each are discussed in a recent review.[10] None of these technologies have reached clinical trials yet, but it is likely we will be confronted quite soon with the safety and efficacy of strategies like PLGA, porous particles and the molecules they will carry.

Medicines in Development for Older Americans

According to a 2014 report by the Pharmaceutical Research and Manufacturers of America (PhRMA), there are 435 new medicines in development for the 15 leading chronic conditions affecting the Medicare population.[13] The condition with the most drugs in development is diabetes with 110 drugs. Then in order, Alzheimer's (67 drugs), arthritis (62), heart disease (61), and COPD (40). The stage of development of the 40 COPD drugs in development is about the same as that of other drugs, namely, from phases I, II, III, and submitted to the FDA respectively, 30%, 43%, 21%, and 6%.[13] One does not know how many potential COPD drugs are in preclinical stages.

According to PhRMA, the novel classes of drugs/agents in development for COPD are stem cells, 2 CXCR2 antagonists, an inhaled p38 inhibitor, a neutrophil elastase inhibitor, an anti-IL-5R monoclonal, several inhaled antibiotics (mostly for bronchiectasis), an IL-17A modulator, a soluble epoxide hydrolase inhibitor, 3 p38kinase inhibitors (one of them oral), a cathepsin C inhibitor, an anti-IL-1R monoclonal, a thromboxane A2 synthase inhibitor, and 4 drugs whose action have not been disclosed.[13] These are mostly drugs that will address inflammation. However, about half of the drugs in development for COPD are monotherapies, fixed combinations, or dual-action agents of classes that have been available for some years. Indeed, all but 3 are in late stage or have since been approved. By contrast, all but 2 of the non-bronchodilator, non-ICS agents were in early stage development, the stages when most drug discontinuations occur. Consequently, older Americans are not likely to ever benefit clinically from their use.

Asthma and COPD Overlap Studies

Studies of patients with the combination of asthma and COPD are beginning to show up on clinicaltrials.gov. A phase II study entitled "Study Assessing Utility of a Clinical Questionnaire to Identify Subjects With Features of Both Asthma and Chronic Obstructive Pulmonary Disease (COPD)" aims to explore and identify the characteristics of ACOS (NCT02302417).[14] The joint primary outcomes are lung function and the ACOS questionnaire which is designed to clinically differentiate patients with ACOS from patients who have either asthma alone or COPD alone. Reversibility of lung function will be used for the latter purpose. Enrollment of 1000 patients was planned and the trial was due to close in May this year.

Another ACOS study (NCT02413359) sponsored by AstraZeneca is being conducted entirely in Japan.[15] The study, which is observational and cross-sectional, has enrolled patients diagnosed as having COPD by GOLD criteria, and attempts to determine how many of them also qualify for the diagnosis of asthma using GINA criteria. Acute exacerbations and evidence of eosinophilic inflammation are items of interest. A total 1100 individuals were to be enrolled and the estimated completion date is July 2015.

Danirixin

Danirixin (GSK1325756) is described by its sponsor as a small, high-affinity, selective and reversible CXCR2 antagonist that inhibits neutrophil transmigration and activation to areas of inflammation. It is in 4 clinical trials, phases I and II, in which its safety, bioavailability and inter-subject variability will be examined. The phase IIb study will be conducted in 2 parts. Part A will be a 2-week open label study to obtain pharmacokinetic data and safety information of repeat dosing of danirixin in approximately 10 patients with COPD. Following a review of the data, Part B will be a 52-week, randomized, double-blind (sponsor unblinded), placebo-controlled parallel group study to evaluate clinical efficacy and frequency of acute exacerbations and respiratory symptoms. Approximately 100 individuals will be

enrolled (NCT02130193).[16]

Biosimilars

The biosimilar product Zarxio by Sandoz, was recently approved as the first biosimilar product to receive approval in the United States. It received the same indication as Amgen's neupogen which is to boost white cell production. The search term *biosimilar* pulls up 102 entries in clinicaltrials.gov but none of them refer to COPD, emphysema or chronic bronchitis. One hopes that will soon change.

Low-Dose Theophylline

A trial of low-dose theophylline was announced in June 2015 although the trial has been in progress for a year or more.[17] The Theophylline with Inhaled Corticosteroids trial investigates whether the addition of low-dose maintenance theophylline (Uniphyllin MR 200 mg tablet once or twice daily) to inhaled corticosteroids has clinical and cost-effective benefits in COPD. A total of 1424 participants with COPD will be randomized to receive either ICS plus theophylline or ICS without theophylline for 52 weeks. The primary outcome is the number of patient-reported acute exacerbations of COPD.

Resunab™

Resumab, also known as JBT-101, is, according to its sponsor Corbus Pharmaceuticals a nanomolar cannabinoid agonist which activates the CB2 receptor present on immune cells and fibroblasts. Upon binding CB2, JBT-101 stimulates the production of specific lipid mediators (PGJ2, LXA4) which act to turn off inflammation and fibrosis.[18] A phase II safety trial has just been initiated enrolling patients with cystic fibrosis (NCT02465450). The agent is also being studied for scleroderma and dermatomyositis.

QBW251

A Novartis drug, QBW251, is about to begin a Phase II clinical trial in COPD. The agent's category is described as being a CFTR modulator similar to the '-caftor' agents already approved for cystic fibrosis. Ninety adults with GOLD stage II and III COPD and a smoking history of 10 pack years or more will be enrolled. They must have chronic bronchitis and must not have emphysema. The trial will be randomized, double blind and placebo controlled. The drug is taken orally twice a day. The primary outcome is the lung clearance index as measured by nitrogen washout at 29 days, but a variety of other lung functions, pharmacokinetics and safety are also outcomes (NCT02449018). As a CFTR modulator, the agent is also being studied in cystic fibrosis patients who have at least one copy of the F508del mutation (NCT02190604).

Aspirin for Emphysema?

In a presentation at the 2015 American Thoracic Society International Conference, Carrie Aaron, MD, presented results of a prospective observational study of aspirin versus no aspirin in 4500 individuals who had emphysema quantified by computed tomography (CT) examination as part of the Multi-Ethnic Study of Atherosclerosis Lung Study.[19] Each individual was studied by CT 4 times over 10 years. The results showed that emphysema progressed more slowly in those who received aspirin 3 or more times per week. The effect was greatest in individuals who had more emphysema at baseline.

Top 10 Prescribed Drugs

The top 10 prescribed drugs in the first 3 months of 2015 includes 3 drugs for COPD, ventolin (ranked number 3), Advair (number 5), and Spiriva (number 9). Symbicort is number 13.[20]

Acknowledgements

Information regarding endobronchial devices kindly provided by Charlie Strange, MD. Many of the items in this report were due to the generous support of Clinical Trials Magnifier Weekly.

Declaration of Interest

Dr. Gross is an advisor to Mylan but has received no information of any kind about TD-4208 from that corporation or from elsewhere.

References

1. Product overview: Redirecting airflow to redirect outcomes. Olympus Respiratory America website. http://www.spiration.com/us/product-overview . Published 2015. Accessed July 9, 2015.
2. Zephyr® endobronchial valve. Pulmonx website. https://pulmonx.com/ous/products/zephyr-endobronchial-valve/ Accessed July 9, 2015.
3. Empysema and RENEW. PneumRx website. http://pneumrx.com/us/healthcare-professionals . Published 2015. Accessed July 9, 2015.
4. Innovation in every breath-Intervapor Precision Ablation. Uptake Medical website. http://www.uptakemedical.com/ Accessed July 14, 2015.
5. A prospective multi-center clinical study to E\evaluate the safety and effectiveness of the OL-BF-001 for severe emphysema-NCT02470052. National Institutes of Health Clinical Trials website. https://clinicaltrials.gov/ct2/show/NCT02470052?term=NCT02470052&rank=1 Published June 2015. Accessed July, 2015.
6. Theravance Biopharma announces positive top-line results from phase 2b dose-ranging study of its investigational LAMA, TD-4208, for the treatment of COPD [news release]. San Francisco, CA: Theravance Biopharma investor relations; September 8, 2014. http://investor.theravance.com/releasedetail.cfm?releaseid=869695 Accessed July 14, 2015.
7. Theravance Biopharma, Inc. and Mylan partner to develop and commercialize a novel LAMA compound, TD-4208, for COPD [news release]. George Town, Grand Cayman Islands and Pittsburgh, PA: Theravance Biopharma investor relations; February 2, 2015. http://investor.theravance.com/releasedetail.cfm?releaseid=893981 Accessed July 14, 2015.
8. GSK product development pipeline. GlaxoSmithKline website. https://www.gsk.com/media/621672/product-pipeline-2015.pdf Published March 2015. Accessed July 14, 2015.
9. Considerations for the design of early-phase clinical trials of cellular and gene therapy products. Guidance for industry. Food and Drug Administration website. www.fdanews.com/06-15-CGTproducts.pdf. Published June 2015. Accessed July 14, 2015.
10. Liang Z, Ni R, Zhou J, Mao S. Recent advances in controlled pulmonary drug delivery. *Drug Discovery Today*. 2015; 20(3):380-389. doi: http://dx.doi.org/10.1016/j.drudis.2014.09.020
11. Ungaro F, d'Angelo I, Miro A, LaRotonda MI, Qualia F. Engineered PLGA nano- and micro-carriers for pulmonary delivery: challenges and promises. *J Pharm Pharmacol*. 2012;64(9):1217-1235. doi: http://dx.doi.org/10.1111/j.2042-7158.2012.01486.x
12. Edwards DA, Hanes J, Caponetti G, et al. Large porous particles for pulmonary drug delivery. Science. 1997;276(5320):1868-1872 . doi: http://dx.doi.org/10.1126/science.276.5320.1868
13. Medicines in development for older Americans: 2014 report. Pharmaceutical Research and Manufacturers of America (PhRMA) website. http://www.phrma.org/sites/default/files/pdf/2014-meds-in-dev-older-americans.pdf Published 2014. Accessed July 14, 2015.
14. Study assessing utility of a clinical questionnaire to identify subjects with features of both asthma and chronic obstructive pulmonary disease (COPD). National Institutes of Health Clinical Trials website. https://clinicaltrials.gov/ct2/show/NCT02302417 Published 2014. Updated 2015. Accessed July 14, 2015.
15. High risk populations among COPD patients in Japan. National Institutes of Health Clinical Trials website. https://www.clinicaltrials.gov/ct2/show/NCT02413359 Published April 2015. Updated May 2015. Accessed July 14, 2015.
16. Investigation of safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical efficacy of oral danirixin in symptomatic COPD subjects with mild to moderate airflow limitation at risk for exacerbations. National Institutes of Health Clinical Trials website. https://clinicaltrials.gov/ct2/show/NCT02130193. Published 2013. Updated July 2015. Accessed July 14, 2015.
17. Devereux G, Cotton S, Barnes P, et al. Use of low-dose oral theophylline as an adjunct to inhaled corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease: study protocol for a randomised controlled trial. *Trials*. 2015;16:267. doi: http://dx.doi.org/10.1186/s13063-015-0782-2
18. Resunab™. Corbus Pharmaceuticals web site. http://www.corbuspharma.com/product-pipeline/resunab. Published 2015. Accessed July 16, 2015.
19. Effects of aspirin use on emphysema. CHEST Video Conference Reporter: ATS Meeting 2015. Medpage TODAY website. http://www.medpagetoday.com/CHESTVideoConferenceReporterATS/special-reports/ATS2015Video-Videos/1141?xid=nl_mpt_CHESTVIDEO_2015-05-18&eun=g5386335d29r. Published 2015. Accessed July 14, 2015.
20. Brown T. The 10 most-prescribed and top selling medications. WebMD website. http://www.webmd.com/news/20150508/most-prescribed-top-selling-drugs Published May 8, 2015. Accessed July 14, 2015.