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Drugs to treat COPD, such as Spiriva, aim to relax the smooth muscle of the airways.

THERAPEUTICS

Strength in numbers

Several new drugs for treating chronic obstructive pulmonary disease are about to hit the market, with more in the pipeline.

BY DUNCAN GRAHAM-ROWE

Shortness of breath, a tightening of the chest, wheezing and that desperate feeling that you can't get enough air into your lungs: these are all familiar to asthma sufferers. For people with chronic obstructive pulmonary disease (COPD), however, such symptoms are not fleeting. They are constant and aggravated by a steady build-up of sputum, shallow breathing and a persistent cough. The most that patients can hope for in terms of treatment is merely to manage their symptoms as they steadily worsen over time.

COPD, unlike asthma, is associated with tobacco smoking and long-term exposure to airborne toxicants, which irreparably damage the lungs, causing inflammation and airway narrowing. But traditionally, COPD has been treated in much the same way as asthma. For relief, patients can inhale short-acting bronchodilators, which relax the airways: for example, salbutamol, which is marketed as Ventolin by the London-based drug giant GlaxoSmithKline (GSK). Inhaled corticosteroids also reduce inflammation in the lungs and therefore decrease the risk of acute episodes known as exacerbations, which can leave patients hospitalized for days. For managing symptoms over the longer term, there are bronchodilator–corticosteroid combinations such as salmeterol–fluticasone propionate (Advair; also marketed by GSK), which can ease symptoms for up to 12 hours. Another long-term option is tiotropium bromide (Spiriva), which acts by a different bronchodilation mechanism to provide 24-hour relief, and is marketed by pharmaceutical companies Boehringer Ingelheim, based in Germany, and Pfizer, based in Groton, Connecticut.

Now, several new drugs for COPD treatment are on the verge of being approved by regulatory authorities (see 'Long-acting, daily medications'). The new candidates are not cures, but they may offer genuine hope that COPD sufferers can have a better quality of life.

FAST ACTION

On the surface, the offerings look like simple replacements for Spiriva and Advair. The closest to market is glycopyrronium bromide (NVA237; Seebri), which is awaiting approval in Europe and has been developed by the pharmaceutical giant Novartis, headquartered in Basel, Switzerland. Like Spiriva, this once-daily drug acts on a set of nerves in the smooth muscle around the airways. "Acetyl-choline acts on muscarinic receptors found in the muscles surrounding the airways, causing the muscle in the airways to contract and the airways to narrow," explains Dave Morris, who heads global development for primary care at Novartis. In patients with COPD, the new drug competes with acetylcholine, blocking the receptors and preventing the airways from closing up. It is therefore classified, together with Spiriva, as a long-acting muscarinic antagonist (LAMA).

Novartis has carried out three large-scale phase III trials of Seebri. In May 2012, it reported the results of the second trial, GLOW2, at the American Thoracic Society International Conference in San Francisco, California. GLOW2 was conducted over one year and involved 1,066 individuals: Seebri not only improved lung function to the same extent as its analogue, Spiriva, but also took effect quicker. At both 5 minutes and 15 minutes after inhalation, it produced a doubling in FEV_1, the amount of air that can be exhaled in 1 second (as measured by blowing into a spirometer). It has also been clinically shown to produce greater bronchodilation in the first 4 hours of use than Spiriva.

GSK is taking a different tack. In July, together with Theravance, a biopharmaceutical company based in South San Francisco, California, it applied for regulatory approval in both Europe and the United States for a new drug combination: vilanterol–fluticasone furoate (previously known as Relovair but now called Relvar or Breo). Relvar is similar to Advair in that it consists of a long-acting β2-agonist (LABA) bronchodilator and an inhaled corticosteroid. Like Seebri (and Spiriva), Relvar works on the nerves in the smooth muscles, but it does so by stimulating β2-adrenergic receptors, which triggers a biochemical cascade that leads to the relaxation of the smooth muscle in the airways. In phase III trials, Relvar improved lung function compared with placebo or Advair when taken over a 12-week period, as measured by standard spirometry tests.

GSK has not yet published numbers showing the extent of the improvement. But, according

LONG-ACTING, DAILY MEDICATIONS

Do combination therapies really add value to COPD treatments? The pros and cons of long acting therapies in the pipeline.

Name	Main benefit	Type of drug	Active components	Delivery method	Doses per day	Adverse effects	Stage
Advair	Improves lung function for a period of time	Long-acting β2-agonist (LABA) and corticosteroid	Fluticasone/ salmeterol	Dry powder inhaler	2	Increased risk of non-fatal pneumonia	Available
Spiriva	Improves lung function for a period of time	Long-acting muscarinic antagonist (LAMA)	Tiotropium bromide	Dry powder inhaler	1	Hives, rash, swelling and dry mouth	Available
PT003	Efficient delivery, improved lung function	LAMA + LABA (two molecules)	Glycopyrrolate and formoterol (LAMA + LABA)	Metered dose inhaler (MDI)	2	Headache, dry mouth and coughing	Phase II completed and Phase III to begin 2013
NVA237	Improves breathing in a matter of minutes	LAMA	Glycopyrronium bromide (LAMA)	Dry powder inhaler	1	Headache, dry mouth and coughing	Phase III completed and approval sought in Europe
Relvar	Once daily instead of twice	LABA + inhaled corticosteroid	Vilanterol and fluticasone furoate	Dry powder inhaler	1	Fatal pneumonia reported	Phase III completed and approval sought in USA and Europe
MABA	Dual action molecule improves lung function	LAMA + LABA	MABA	Most likely dry powder inhaler	Unknown	Unknown	Phase II

to a spokesperson, Relvar's effects last longer than those of Advair, so it need only be taken once a day rather than twice. A once-daily dose should significantly increase compliance. "Patients frequently don't take their second dose," says James Donohue, a pulmonary diseases specialist at the University of North Carolina at Chapel Hill, who has been involved in trials of Spiriva and has worked as a consultant to both GSK and Novartis.

DYNAMIC DUOS

Patient compliance concerns are also driving the development of combination therapies — the rationale being that patients find it easier to take a single medication. Combination therapies also have another advantage. Inhaled corticosteroids don't seem to have strong anti-inflammatory effects when they are used in isolation. When used in conjunction with separate bronchodilators, however, they've been shown to reduce the frequency of exacerbations. This synergistic effect probably arises because "the β-agonist facilitates the entry of the steroid into the [cell's] nucleus", Donohue says. So delivering them as part of a combination therapy has the potential to optimise this synergy.

Another effect with ramifications for treating COPD involves the simultaneous use of a LAMA and a LABA. The idea is to open the airways further by simultaneously switching off the nerves that tighten the passages while stimulating the ones that relax them, says Chris Cates, a population health researcher at St George's University of London who studies COPD.

Such LAMA–LABA combinations are being developed by a company called Pearl Therapeutics, based in Redwood City, California. Pearl has already carried out eight clinical trials on a combination therapy called PT003, and phase III trials are set to commence in the first half of 2013, says Colin Reisner, Pearl's chief medical officer.

PT003 is notable not so much for its chemistry as for its novel method of delivery, says Donald Tashkin, medical director of the Pulmonary Function Laboratory at the David Geffen School of Medicine, University of California, Los Angeles, who has consulted for the company. Both the LAMA and LABA components — glycopyrrolate and formoterol fumarate, respectively — are established drugs. But PT003 delivers them together, bound to particles with a diameter of less than 5 micrometers. In this way, the drug molecules are suspended in solution and can be dispensed through a metered dose inhaler, a device that many patients find easier to operate than the commonly used dry powder inhalers. The molecular vehicle also provides an efficient means of delivery, ensuring that around half of the drug reaches its target, as opposed to as little as 5% with some delivery systems, says Tashkin.

Synergistic effects can occur in the lungs even when LABAs and LAMAs are inhaled separately, but one after the other. However there is preclinical evidence that the approach of administering them simultaneously through a single device, as for PT003, may enhance their effect even further, says Darrell Baker, a senior vice president who oversees GSK's respiratory portfolio.

"The big question of drug combinations is whether the costs outweigh the benefits."

If this is the case, then another novel drug, being developed jointly by GSK and Theravance, could prove successful. The drug is a single molecule with both LAMA and LABA properties. Phase II clinical trials of this muscarinic antagonist–β2 agonist (MABA) have been promising, says Baker, which when compared to salmeterol "improved bronchial dilation across a range of doses".

Even so, no trial data have been released so far, and the company's plans for this MABA are unclear. "We are keen to see how it works as a bronchodilator by itself," says Baker. "However, we also see the opportunity for a triple-mechanism action with an inhaled corticosteroid."

Ultimately, this is where the greatest value may lie — not in the pharmacological precision of a single molecule with a dual mechanism of action, but rather in the ease with which it could pass through the drug regulatory system. "The beauty of this is when it is approved, MABA would count as one drug," says Baker.

In principle, companies hoping to develop a triple therapy by adding one drug to this MABA would therefore have a low regulatory bar, says Tashkin. Normally, triple combination therapy would require a six-way study — demonstrating improvement over not just the individual constituents but also their various combinations — but combining the MABA with an inhaled corticosteroid would require a simpler burden of proof.

The big question, says Cates, is whether the costs outweigh the benefits. For instance, adding corticosteroids may lower the risk of exacerbations but increase the risk of pneumonia. Indeed, there have been fatal cases of pneumonia associated with Relvar (although it is not the only drug to carry that potential risk). According to Baker, the company is likely to market the drug at lower doses than those given to trial subjects who developed pneumonia.

Although many of these new drug candidates hold promise and have short-term benefits, none of them has yet been shown to improve lung function year on year, says Cates. So until drug companies start to find ways to help repair damaged lungs and reverse the effects of COPD, there is only one long-term 'treatment' available to patients, he adds, and it does not involve taking drugs but abstaining from them: quitting smoking. ■

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