New drugs

Glycopyrronium bromide

Approved indication: chronic obstructive pulmonary disease

Seebri breezhaler (Novartis)

capsules containing 50 microgram powder for inhalation

Australian Medicines Handbook section 19.1.2

Long-acting bronchodilators have a role in the maintenance treatment of patients with symptomatic chronic obstructive pulmonary disease (COPD). One option is a long-acting anticholinergic drug and prescribers can now choose between tiotropium and glycopyrronium bromide.

Glycopyrronium is not a new drug. Also known as glycopyrrolate, an injectable form has been used by anaesthetists to dry up secretions. It blocks acetylcholine at muscarinic receptors. In the lung, acetylcholine acts on smooth muscle to cause bronchoconstriction, so antagonising this with inhaled glycopyrronium will result in bronchodilation. This begins within five minutes and is sustained for 24 hours.

After the dry powder is inhaled, using a specific device, about 40% is absorbed, mainly through the lungs. Most of the absorbed dose is excreted in the urine. After inhalation the elimination half-life is 33–57 hours. Clearance will be reduced by renal disease, but no dose reduction is recommended for patients with a glomerular filtration rate above 30 mL/min/1.73 m^2.

The approval of glycopyrronium is based on two main trials, GLOW 1[1] and GLOW 2[2]. Both trials assessed lung function in patients over 40 years old with a smoking history of at least 10 pack-years. These patients had moderate-to-severe COPD with a forced expiratory volume in one second (FEV_1) that was under 80%, but more than 30%, of the predicted value after bronchodilation. Approximately 50% of the patients were using inhaled corticosteroids.

In GLOW 1, 552 patients were randomised to inhale 50 microgram glycopyrronium once daily while 270 were randomised to take a placebo. Although the trial was for 26 weeks, the primary outcome was a measurement of mean trough FEV_1 at 12 weeks. At the start of the trial the mean post-bronchodilator FEV_1 was 1.49 L in the glycopyrronium group and 1.45 L in the placebo group. The FEV_1 improved from the first day of active treatment. After 12 weeks the trough FEV_1 (measured just before the next dose) was 1.408 L with glycopyrronium and 1.301 L with placebo. The 108 mL difference in FEV_1 is statistically significant and the advantage over placebo was still present at 26 weeks.[1]

GLOW 2 was also placebo controlled, but also included an open-label tiotropium arm. There were 529 patients randomised to take glycopyrronium, 269 to take placebo and 268 to take tiotropium (18 microgram once daily). All the patients had a mean post-bronchodilator FEV_1 of 1.5 L at the start of the 52-week study. The primary outcome measure was the mean trough FEV_1 at 12 weeks. These values were 1.469 L for glycopyrronium, 1.455 L for tiotropium and 1.372 L for placebo. The advantage over placebo, 97 mL for glycopyrronium and 83 mL for tiotropium, was statistically significant.[2]

The GLOW trials studied several secondary outcomes. Compared to placebo, glycopyrronium reduced dyspnoea and the risk of exacerbations.[1,2] The smaller GLOW 3 trial showed improved exercise tolerance after three weeks in 55 patients who took glycopyrronium compared with the 53 who took placebo.[3]

As glycopyrronium is a muscarinic receptor antagonist it has predictable anticholinergic adverse effects. Dry mouth is the most common and there is a possibility of precipitating urinary retention and narrow-angle glaucoma in susceptible patients. Although it is uncommon, some patients develop atrial fibrillation. Inhaling a dry powder can cause coughing and throat irritation. There are no studies of pregnant or lactating women.

Inhaled glycopyrronium has a greater effect than placebo, but more experience is needed to see if improvements in lung function lead to improved clinical outcomes. Many patients will not respond. In a pooled analysis of GLOW 1 and GLOW 2 the proportion of patients with a clinically meaningful improvement (≥100 mL) in trough FEV_1 was 52% at week 12 and 49.7% at week 26. After a year only 42.5% of patients had a clinically meaningful improvement. Similarly, many patients' symptoms did not improve significantly. After 26 weeks, 57.8% of patients had a clinically relevant improvement in their quality of life compared with 61% of the tiotropium group and 47.6% of the placebo group.[4] GLOW 3 showed a significant benefit, but the absolute improvement in exercise endurance compared to placebo was under 90 seconds.[3]

Although glycopyrronium has an early onset of effect, it is not approved for acute bronchospasm. On current

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

evidence, glycopyrronium does not seem to have any advantages over tiotropium.

X manufacturer did not respond to request for data

REFERENCES †A

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)