Glycopyrronium (Seebri Breezhaler): once-daily LAMA for COPD

Steve Chaplin BPharm, MSc and **Alice Turner** PhD, MRCP

Glycopyrronium is a new LAMA for maintenance treatment of COPD. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse events and Dr Alice Turner discusses its place in therapy.

KEY POINTS

- glycopyrronium (Seebri Breezhaler) is a long-acting once-daily inhaled antimuscarinic for the symptomatic treatment of COPD in adults
- it is administered via a single 50µg capsule loaded into a dry-powder inhaler (Breezhaler)
- 6 capsules plus inhaler cost £5.50; 30 capsules plus inhaler cost £27.50 (compared with £33.50 for Spiriva HandiHaler – 30 capsules refill)
- in clinical trials lasting 6–12 months in patients with moderate to severe COPD, glycopyrronium improved lung function, reduced breathlessness and improved symptoms, and it reduced moderate to severe exacerbations
- glycopyrronium appears to be as effective as tiotropium
- a study suggests that more patients prefer the Breezhaler to the HandiHaler

The NICE 2010 guideline on the management of COPD states that the objectives of treatment are improvement in lung function, symptoms, activities of daily living, exercise capacity and onset of symptom relief.[1] It recommends initial treatment with a short-acting bronchodilator (beta-agonist or antimuscarinic) taken as required.

Patients with stable mild to moderate COPD (FEV_1 ≥50 per cent predicted) who remain breathless or have exacerbations should be offered an inhaled once-daily long-acting antimuscarinic (LAMA) or a long-acting beta-agonist (LABA). If a LABA alone is unsuccessful, an inhaled steroid may be added (in a combined inhaler) or, if a steroid is not suitable, a LAMA may be added.

The options for those with severe COPD (FEV_1 <50 per cent predicted) or frequent exacerbations are a LABA plus inhaled steroid in a combination inhaler or a LAMA.

For all patients, regardless of lung function, a LAMA should be combined with LABA/steroid if they remain breathless or have exacerbations despite either option alone.

Until the advent of glycopyrronium bromide (Seebri Breezhaler), the available LAMAs were tiotropium bromide (Spiriva) and aclidinium bromide (Eklira Genuair).

The technology

Glycopyrronium bromide is a LAMA with a rapid onset (five minutes) and a 24-hour duration of action. It is licensed as a maintenance bronchodilator to relieve symptoms in adults with COPD. The recommended dose is 50µg glycopyrronium once daily, which is administered via a single capsule loaded into a dry powder inhaler (Breezhaler); the delivered dose from this is 44µg.

No dose adjustment is recommended for elderly patients or those with mild to moderate renal failure. Glycopyrronium is predominantly excreted renally and should be used in patients with severe renal disease or who are undergoing dialysis only when the benefits exceed the risks. There is no experience of its use in patients with hepatic impairment or cardiovascular disease.

As with other antimuscarinic agents, it should be used with care in patients with narrow-angle glaucoma or urinary retention.

No clinically significant interactions have been identified.

Clinical trials

Two phase 3 trials provide the key clinical evidence for glycopyrronium: GLOW1 (glycopyrronium bromide in COPD airways clinical study 1)[2] and GLOW2 (study 2).[3] Both included adults aged at least 40

with moderate to severe COPD (FEV_1 30–79 per cent predicted) and a smoking history of at least 10 pack years. Previous long-acting bronchodilator therapy was discontinued. The primary end-point in both was trough FEV_1 after 12 weeks of treatment. Secondary end-points included breathlessness, health status, exacerbation rate and symptoms.

Patient characteristics in the two trials were similar. Mean age was 64. Approximately 60 per cent had moderate COPD, with mean baseline FEV_1 54–56 per cent predicted. In the preceding year, 16–20 per cent reported one exacerbation and 5–7 per cent reported at least two. About half were using an inhaled steroid.

GLOW1 randomised 822 patients to treatment with glycopyrronium or placebo. About 20 per cent of patients in each group discontinued treatment early; of these, about 30 per cent in each arm of the study were due to adverse effects.

At week 12, mean trough FEV_1 was significantly higher among patients treated with glycopyrronium (1.408 *vs* 1.301 litres with placebo). This difference was maintained after six months' treatment. There was a clinically significant improvement in breathlessness at six months (measured by the transition dyspnoea index). The mean improvement in health status score (by the St George's Respiratory Questionnaire) with glycopyrronium was statistically but not clinically significant compared with placebo, though the proportion of patients with clinically significant improvement was greater (57 *vs* 46 per cent).

The incidence of moderate or severe exacerbations was significantly lower with glycopyrronium (18 *vs* 24 per cent with placebo) and it also reduced admissions due to severe exacerbations (hazard ratio, HR, 0.35; CI 95% 0.141–0.857; p=0.022). Patients treated with glycopyrronium used a mean of 0.46 per day fewer puffs of rescue medication.

In GLOW2, 1066 patients were randomised to one year's treatment with glycopyrronium, placebo or open-label tiotropium (the study was not powered to demonstrate that glycopyrronium was superior to tiotropium). The proportions of patients discontinuing active treatment were similar (22–23 per cent *vs* 28 per cent with placebo)

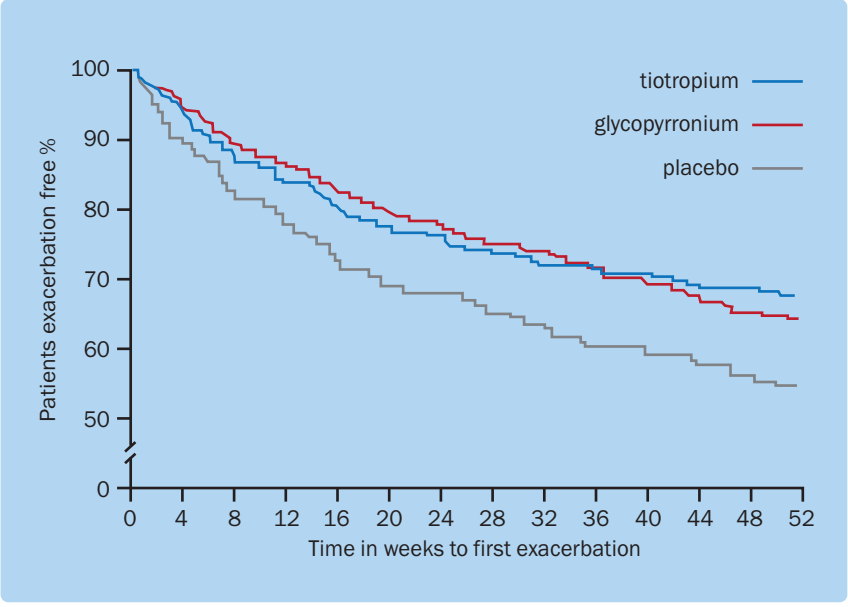

Figure 1. Time to first moderate to severe exacerbation in GLOW2; after reference 3

After 12 weeks, mean trough FEV_1 was significantly higher with glycopyrronium (1.469 litre) and tiotropium (1.455 litre) than placebo (1.372 litre); these differences were maintained at 12 months though lung function declined in all groups (FEV_1 1.412, 1.392 and 1.303 litre respectively at 12 months).

Glycopyrronium and tiotropium improved breathlessness and health status scores at 3, 6 and 12 months compared with placebo, and to a similar extent. Compared with placebo, the rate of moderate to severe exacerbations was significantly lower with glycopyrronium (rate ratio 0.66; CI 95% 0.49–0.86) but not tiotropium (rate ratio 0.80; CI 95% 0.58–1.10). Time to first exacerbation was significantly increased by both drugs compared with placebo (see Figure 1). Glycopyrronium reduced the use of rescue medication by a mean of 0.37 puffs per day; tiotropium did so by 0.66 puffs (both statistically significant *vs* placebo).

A short study has shown that glycopyrronium increased exercise time compared with placebo in 108 patients. Statistically significant improvement was evident after one day and, after three weeks, mean exercise endurance time (measured by a cycling test) was increased from 417 seconds with placebo to 506 seconds with glycopyrronium.[4] This was associated with statistically significant improvements in leg discomfort and exertional breathlessness.

Adverse effects

The adverse effects of glycopyrronium are typical of an inhaled antimuscarinic agent, the commonest being dry mouth (about 2 per cent *vs* 1 per cent with placebo).[5] Benign prostatic hyperplasia was not reported in patients assigned to placebo but it was present in 0.3 per cent of those treated with glycopyrronium and 0.8 per cent of those taking tiotropium.

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Declaration of interests

None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

Place in therapy

Until recently there was only one inhaled LAMA on the market (tiotropium), but two others have recently been licensed (glycopyrronium and aclidinium). So why the need to develop any other LAMAs?

Firstly, other compounds might be more effective or have fewer side-effects than tiotropium. Secondly, it gives choice, a key concept in the NHS and an important one when it comes to inhalers as there are marked differences in technique with each LAMA device, and there will be patients that use one better than another. Tiotropium, for example, already has two available devices.

Why choose glycopyrronium?

Glycopyrronium is a once-daily LAMA. Like tiotropium it has a sustained 24-hour bronchodilator effect[1] but higher selectivity for the M_3 than for the M_2 muscarinic receptor.[2] Blocking the M_3 causes bronchodilatation while blocking M_2 leads to tachycardia, thus it might be expected to have fewer cardiac side-effects.

Dissociation from the M_3 receptor occurs four times faster than tiotropium[2] and almost twice as fast as aclidinium.[3] This suggests that glycopyrronium would have a more rapid onset of action, which has been confirmed in clinical studies,[1,4] and could influence adherence.

Few head-to-head trials of LAMAs have been completed with the exception of GLOW2,[1] which demonstrated product equivalence in terms of trough FEV_1, dyspnoea score and exacerbation reduction.

The trial was open label for tiotropium, and powered to detect superiority over placebo, thus has some weaknesses. Nevertheless the data are at least strongly suggestive that the place of glycopyrronium in therapy should be the same as tiotropium, provided the

Trial	Duration	Outcome	Comparator
Tiotropium			
Brusasco V, *et al*, 2003[9]	26 weeks	↓ exacerbations ↑ HRQoL	placebo, salmeterol
Briggs DD, *et al*, 2005[10]	12 weeks	↑ FEV_1	salmeterol
Tashkin DP, *et al*, 2008[11] (UPLIFT)	4 years	↓ exacerbations ↑ HRQoL ↑ FEV_1	placebo
Vogelmeier C, *et al*, 2011[12] (POET)	1 year	↓ exacerbations	salmeterol
Glycopyrronium			
D'Urzo A, et al, 2011[4] (GLOW1)	26 weeks	↑ trough FEV_1 ↑ HRQoL ↓ dyspnoea (TDI score) ↓ exacerbations	placebo
Kerwin EM, *et al*, 2012[1] (GLOW2)	1 year	similar to GLOW1 *vs* placebo ↑ bronchodilatation on day 1 and week 26 *vs* tiotropium	placebo, tiotropium
Beeh KM, *et al*, 2012[13] (GLOW3)	8 weeks	↑ endurance time ↑ inspiratory capacity	placebo
Aclidinium			
Jones PW, *et al*, 2011[14] (ACCLAIM I/II)	1 year	↑ trough FEV_1 ↑ HRQoL	placebo
Jones PW, *et al*, 2011[15] (ATTAIN)	6 months	↑ FEV_1 ↑ HRQoL ↓ dyspnoea (TDI)	placebo
Kerwin EM, *et al*, 2012[16] (ACCORD)	12 weeks	↑ FEV_1 ↑ HRQoL ↓ dyspnoea (TDI)	placebo
Fuhr R, *et al*, 2012[17]	15 days per treatment	similar to ACCORD *vs* placebo ↑morning FEV_1 *vs* tiotropium	placebo, tiotropium

HRQoL = health-related quality of life; TDI = transition dyspnoea index

Table 1. Key clinical trials and clinical outcomes of LAMAs in COPD

patient is able to use the device equally well.

A study of the Breezhaler against the HandiHaler suggested that more patients prefer the Breezhaler.[5]

Glycopyrronium is also cheaper (30 capsules £27.50 *vs* £33.50 for HandiHaler refill). While the saving is not much per patient, at a population level wide use would result in significant NHS cost savings, which seems sensible if the drugs are equally effective.

A summary of clinical effects of LAMAs is shown in Table 1. Tiotropium and glycopyrronium have roughly equal data, while aclidinium lacks such good data on exacerbation reduction, perhaps because severity of COPD in these studies was less and event rates lower.

The Cochrane review of LABAs *vs* LAMAs[6] was only able to consider trials using tiotropium (due to their search dates) and concluded that LAMAs were superior in terms of preventing exacerbations and disease-related hospitalisation.

As such a LAMA should be the first-line maintenance inhaler for COPD patients, unless there is a good reason to choose a LABA, for instance due to the presence of severe glaucoma.

Safety

Clinical trials involving all LAMAs have reported similar total adverse event rates with drug and placebo. Overall the most common adverse event in GLOW2 was COPD exacerbation, which was higher in the placebo arm than others.

Usually the most common adverse events directly due to LAMAs are those attributed to anticholinergic activity, although the most common event in the glycopyrronium arm of GLOW2 was nasopharyngitis.[1]

More recently there has been concern over the cardiovascular safety of LAMAs. This has been reported only in meta-analyses using the tiotropium Respimat device.[7] The recent TIOSPIR study was designed to answer the question over cardiac safety of the Respimat device and compared this to the HandiHaler, enrolling patients with pre-existing stable cardiac disease.[8]

No differences were seen between the two devices, providing some reassurance that LAMAs can be used safely in patients with cardiac co-morbidity.

Conclusion

Glycopyrronium is an effective LAMA that has equal place in COPD therapy with tiotropium.

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Declaration of interests

Dr Turner has received fees for advisory boards, conference attendance and/or educational talks from Boehringer, Novartis, GSK and AstraZeneca, all of who manufacture drugs for COPD.

Dr Turner is clinician scientist and honorary consultant in respiratory medicine, School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham