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REVIEW

Role of nebulized glycopyrrolate in the treatment of chronic obstructive pulmonary disease

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Abstract: In the upcoming years, the proportion of elderly patients with chronic obstructive pulmonary disease (COPD) will increase, according to the progressively aging population and the increased efficacy of the pharmacological treatments, especially considering the management of chronic comorbidities. The issue to prescribe an appropriate inhalation therapy to COPD patients with significant handling or coordination difficulties represents a common clinical experience; in the latter case, the choice of an inadequate inhalation device may jeopardize the adherence to the treatment and eventually lead to its ineffectiveness. Treatment options that do not require particular timing for coordination between activation and/or inhalation or require high flow thresholds to be activated should represent the best treatment option for these patients. Nebulized bronchodilators, usually used only in acute conditions such as COPD exacerbations, could fulfill this gap, enabling an adequate drug administration during tidal breathing and without the need for patients' cooperation. However, so far, only short-acting muscarinic antagonists have been available for nebulization. Recently, a nebulized formulation of the inhaled long-acting muscarinic antagonist glycopyrrolate, delivered by means of a novel proprietary vibrating mesh nebulizer closed system (SUN-101/eFlow®), has progressed to Phase III trials and is currently in late-stage development as an option for maintenance treatment in COPD. The present critical review describes the current knowledge about the novel nebulizer technology, the efficacy, safety, and critical role of nebulized glycopyrrolate in patients with COPD. To this end, PubMed, ClinicalTrials.gov, Embase, and Cochrane Library have been searched for relevant papers. According to the available results, the efficacy and tolerability profile of nebulized glycopyrrolate may represent a valuable and dynamic treatment option for the chronic pharmacological management of patients with COPD.

Keywords: glycopyrrolate, glycopyrronium, nebulizer, COPD, antimuscarinic, device

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by not fully reversible airflow obstruction due to structural derangement of the airways, sustained by an inflammatory response secondary to inhalation of noxious particles, mainly represented by cigarette smoke and air pollutants.[1] COPD represents an increasing social and health care problem, and a leading cause of disability. In current projections, mortality due to COPD will eventually increase by 2030 to become the third most common cause of death worldwide.[2] In COPD, both chronic bronchitis and emphysema can be present with different intensities and are responsible for airway narrowing, mucus hyper-secretion, loss of small conducting airways, and lung elastic recoil.[3] Starting from the peripheral airways, which represent the site of the initial damage, these anatomic changes eventually lead to expiratory airflow limitation, air trapping, dynamic hyperinflation, increased closing volume, and

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ventilation–perfusion mismatch.[4–6] Long-acting muscarinic antagonists (LAMAs), such as tiotropium, aclidinium, glycopyrronium, and umeclidinium, and long-acting β2 agonists (LABAs), such as indacaterol, formoterol, salmeterol, and olodaterol, are able to reduce hyperinflation[7] and the extent of airway closure,[8] improving symptoms and exercise tolerance,[9] and thus represent the cornerstone of the long-term pharmacological treatment in COPD. Although inhaled therapy has the advantage to be administered directly to the site of action, the process interposed between the actuation of the device and the drug deposition in lung periphery relies on numerous variables, namely the drug formulation, patients' inhalation technique, and lung mechanics.[10] So far, the most widespread hand-held inhalers' devices are represented by dry powder inhalers (DPIs), pressurized metered dose inhalers (pMDIs), and soft mist inhalers (SMIs), while nebulizers are often left for the treatment of acute conditions such as COPD exacerbations or in patients with extremely limited self-sufficiency.[11] Although effective, technologically advanced and portable, the use of handheld devices has always been affected by numerous major mistakes that lead to an incorrect inhalation technique and eventually to the lack of treatment efficacy,[10] especially in older patients with COPD, with a severe disease and multiple comorbidities.[10] In the latter group of patients, drug delivery via nebulization may provide an effective alternative, since an optimal dose can be delivered during tidal breathing, regardless of disease severity or associated comorbidities, thus overcoming the need for coordination, specific handling and inspiratory maneuvers.[12]

The present critical review will be focused on the nebulized delivery technology, developmental phases, efficacy and safety of nebulized glycopyrrolate (nebulized glycopyrronium bromide [GBn]) in patients with COPD. Medline, Embase, Cochrane Library, and ClinicalTrials.gov were searched for relevant full papers and conference abstracts up to August 2017. Only manuscripts in English language were considered.

Management issues in COPD treatment

The peculiarity of the pharmacology of the respiratory system is represented by the possibility to grant drug delivery directly to the desired site of action, allowing to bypass the majority of the intermediate metabolic steps usually inevitable for other administration routes.[13,14] However, the efficacious access to the lung is jeopardized by complex variables that range from drug formulation and posology to the pathophysiology and stage of the disease. In this view, adherence becomes crucial for treatment efficacy. In clinical trials, adherence to inhaled treatments is usually >80%,[15] a result that does not usually reflect the real life context, in which adherence can be as low as 10%.[16,17] Reduced adherence does not only impact the daily clinical management of patients with COPD but also increases the frequency of exacerbations, the number of hospitalizations, and emergency department visits, thus negatively affecting health care costs.[18]

The device used to deliver the inhaled drug represents a fundamental step for the clinical decision process and may be as important as the choice of the drug itself. The inhalation devices more commonly prescribed are represented by pMDIs, DPIs, SMIs, and nebulizers. Despite a long-standing debate, there is no consensus on how to match patient requirements with criteria for selecting an alternative inhaler device. Rather than insisting with training a patient with a specific inhaler, it would be more appropriate to match the device with the needs and the skills of the patient.[10] Most of the inhalation devices currently available on the market have a comparable efficacy, provided they are used appropriately.[11,19–21] During drug administration, up to 75% of patients with COPD do not receive an optimal dose of the inhaled drug, mainly because of poor coordination or inhalation techniques.[22,23]

For pMDIs, the most common administration errors are represented by the patient's poor coordination between the device activation and drug inhalation or by a short inhalation time. During DPIs' use, patients are often unable to obtain a sufficient inspiratory peak flow necessary get the resistance required to activate the drug and dissociate the carrier from the active molecule; moreover, common mistakes regard dose preparation and exhalation through the device prior to inhalation.[24–27] Even the use of SMI requires an accurate priming and breathing technique,[28] although the timing for inspiration and the required inspiratory flow are respectively longer and lower compared to pMDIs, since the delivered aerosol lasts three times longer than in pMDIs.[25] DPIs are often sensitive to humidity, which can reduce the delivered dose, while SMIs and pMDIs, when left unused for some time, must be re-primed.[29] Advantages and disadvantage of the devices currently available on the market are summarized in Table 1.

Generally, patients that commit errors during inhalatory therapy hiring, tend to be older, more debilitated and to have a severe disease. In elderly patients, unintentional nonadherence to inhalation therapy often comes from cognitive impairment, hearing or visual loss, and other physical disabilities, such as arthritis and tremors resulting in poor coordination, which significantly affect their ability to

Table 1 Advantages and disadvantages of inhalation devices

Device type	Advantages	Disadvantages
pMDI	– Portable – Does not require preparation – No drug contamination risk – High reproducibility for each actuation – Multidose – High number of drugs to choose	– Needs coordination between inspiration and dose actuation – High oropharyngeal deposition – Does not always indicate the number of doses left – Contain propellants – Need to be re-primed after no use
Ultrafine pMDI	– Portable – Does not require preparation – No drug contamination risk – High reproducibility for each actuation – Multidose – High lung deposition and minor oropharyngeal deposition	– Few drugs to choose – Needs coordination between inspiration and dose actuation – Does not always indicate the number of doses left – Fast expiration if containing formoterol – Needs to be re-primed after no use
Breath-actuated pMDI	– Useful when coordination is lacking – Useful in older age – Does not require spacers	– Needs adequate inhalation effort
DPI	– No coordination required – No propellant needed – Remaining dose counters – Portable – Usually multidose – Short administration time	– Usually requires more steps to prepare the drug prior to inhalation – Some are single-dose – Needs adequate inhalation effort – Higher oropharyngeal deposition – Usually more expensive than pMDIs – Humidity can reduce the released dose – Device declivity for a correct loading dose
SMI	– Easy to use – Portable – Multidose – No propellant needed – Higher actuation duration limiting the effects of poor coordination activation/inhalation	– Needs careful preparation at the first use – Multiple steps involved – Needs to be re-primed after no use
Jet nebulizer	– Easy to use – No need for coordination – Adapt for every age (even <4 years) – Available for oxygen enrichment – Contemporaneous use of different drugs – No propellant needed – Can be used by bedridden patients	– Cumbersome – Noisy – High treatment time – Possibility of microbial contamination – Needs cleaning and periodic maintenance – Needs electricity – Uncertainty of effective dose delivered to the lung
Ultrasonic wave nebulizer	– Easy to use Requires minimal cognitive ability – Lightweight – Silent – No need for coordination – Adapt for every age (even <4 years) – Available for oxygen enrichment – Contemporaneous use of different drugs – No propellant needed – Can be used by bedridden patients	– Possible drug heat degradation – Too much liquid waste – High treatment time – Possibility of microbial contamination – Needs cleaning and periodic maintenance – Needs electricity – Uncertainty of effective dose delivered to the lung
Ultrasonic VMT	Same advantages as ultrasonic nebulizers – Shorter treatment time – High efficiency and less waste – No drug degradation – Battery powered – Easy to clean, disinfect and autoclave – Display delivers feedback during inhalation	– Higher price – Needs cleaning after every use – Not available for contemporaneous use of different drugs – May not readily aerosolize drug suspensions

Abbreviations: DPI, dry powder inhaler; pMDI, pressurized metered dose inhaler; SMI, soft mist inhaler; VMT, vibrating mesh technology.

understand and follow the suggested treatment. Complex pharmacological regimens are also secondary to multiple chronic comorbidities, representing a major risk factor for impaired adherence.[25]

Glycopyrrolate by nebulizer

Taking into account the aging population and the projected increase in the prevalence of respiratory tract diseases, patients with COPD will become older, and treatment options

that do not require an optimal coordination for activation/inhalation or require a flow threshold to be activated will become the preferable treatment option.

To date, nebulized muscarinic antagonists are limited to short-acting formulations (SAMAs), while β-agonists are available both as short-acting (SABAs) and as long-acting formulations (aformoterol tartrate), the latter approved only in the USA. SAMA and SABA, in addition to being the treatment choice in acute conditions, are also often suggested for maintenance treatment in selected COPD patients. However, to maintain an optimal bronchodilation coverage, three or four doses per day are needed when SAMA and SABA are delivered via a general purpose jet nebulizer. The latter are usually bulky, characterized by limited portability and with dispensing times of 10–15 minutes per dose, aspects that likely affect patients' compliance. In view of the aforementioned limitations, the lack of long-acting molecules that would reduce the daily posology and a shorter delivery time appear desirable.[30]

The GOLD document recommends nebulizers to be used in specific populations, such as patients with inspiratory flow rates as low as <30 L/s or patients with poor hand-eye coordination.[1] Furthermore, the benefits of nebulizer treatment over DPI and MDI formulations should be evaluated symptomatically and the treatment should be continued as long as similar benefits are not achievable by simpler, cheaper, and more portable alternatives. Indeed, recent surveys reported both patients and their caregivers to be increasingly satisfied with nebulized drug delivery, in terms of symptom relief, ease to use, and improved quality of life.[10,11,31]

Nebulizers can convert a liquid into aerosol droplets suitable for patient inhalation. Currently, the technologies available are mainly represented by air-jet nebulizers, the most widely used, and ultrasonic nebulizers. There are also two pysicochemical categories of drugs available for nebulization: solutions and suspensions. Solutions contain a drug dissolved in saline or other liquids. Suspensions contain a drug that is not soluble in water or other respirable liquids but exist as a mixture of small drug particles suspended in liquid, which jeopardizes their presence in each droplet generated during the nebulization process. Conventional ultrasonic nebulizers cannot be used to administer suspensions.[30]

Due to their safety profile and to a better exacerbation-preventing effect compared to LABAs,[32,33] LAMAs are usually the preferred starting therapy for COPD patients, but no nebulized LAMA is actually available on the market. As a part of the maintenance treatment of patients with COPD, in last years, glycopyrronium bromide (GB) has been developed and available as a single agent, in combination with LABAs,[34–36] or in triple therapy in fixed dose combination with LABAs and inhaled corticosteroids (ICSs).[37,38] The effects of GBn have been studied since 1984 in patients affected by asthma and since 1995 in patients with COPD.[39,40] Interestingly, probably due to its limits in administering time and portability, nebulization was the first to be studied, but the least to be proposed on the market. In the last years, several clinical trials have investigated a nebulized formulation of GBn delivered by a high efficiency nebulizer, which is currently awaiting for the US Food and Drug Administration (FDA) approval as maintenance therapy in COPD patients.

GBn has been investigated as a soluble molecule named EP-101 in 2015.[41] Later on, under the name of SUN-101, it was part of the Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer (GOLDEN) development program, consisting of a total of seven trials.[42–48]

GBn was studied to be delivered by the eFlow® Closed System (eFlow® CS) device (PARI Pharma GmbH, Starnberg, Germany). The latter is characterized by the possibility to deliver a wide range of drug volumes (0.5–5 mL) and dosages (0.001–1,000 mg). In addition, the hole sizes can be adjusted from just <2 μm upward, allowing this system to deliver drugs during consecutive breaths. The eFlow® is a vibrating mesh nebulizer, an evolution of 2005 ultrasonic wave nebulizers, in which a mesh/membrane with 1,000–7,000 laser-drilled holes vibrate at the top of the liquid reservoir, pressuring out a mist of very fine droplets through the holes. The latter technology appears to have solved some important issues existent with previous nebulizers, such as having too much liquid waste and undesired heating of the medical liquid. Portability for these devices is also enhanced by the battery-power and lightweight design. A disadvantage of vibrating mesh nebulizers consists of the little information concerning the ideal dose of the bronchodilator solution to be added to the nebulizer; consequently, the potential of over-dosing exists if the same dose for conventional jet nebulizers is used. To address this concern, a new generation of closed system mesh nebulizers has been conceived that will accept only the ampule containing the specific drug approved for use.[49]

In successive trials, a modified version of the eFlow® nebulizer was adopted: the eFlow® CS. The latter is a handheld, portable, battery-operated, electronic vibrating membrane nebulizer, modified from an FDA-cleared open-system device used to deliver cystic fibrosis medications. Like other vibrating mesh nebulizers, the eFlow® is virtually silent,

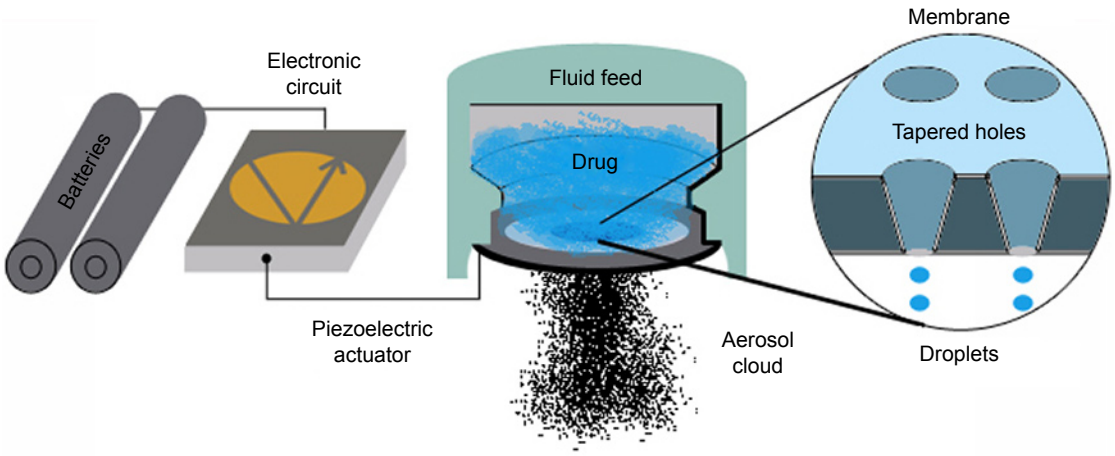

Figure 1 Simplified structure of the eFlow® (PARI Pharma GmbH, Starnberg, Germany) nebulizer.

designed to deliver the medication in two to three minutes during tidal breathing. It has been shown to improve patient compliance due to its comparatively short treatment time since it is more efficient than having a vibrating piezoelectric element at the bottom of the liquid reservoir (Figure 1).[50] The most common jet nebulizers are usually cumbersome, not portable, noisy (up to 60 dB) and require 10–15 minutes to deliver the drug.[51]

Fundamental for the destiny of an aerosolized particle is its aerodynamic diameter, determined by geometrical diameter, density, and form.[52] Only particles with a diameter between 5 and 0.5 µm can reach and stay in the lung: bigger particles impact on upper airways' mucosa, while smaller ones usually reach alveoli but are also exhaled away since they fail to lay on the epithelium.[52,53] The mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and fine particle fraction (FPF, %, <5 µm) of the eFlow® CS system have values independent of formulation strength. For both strengths tested, the mean MMAD was 3.7 µm, the mean GSD was 1.7, and the mean FPF was 72%. As expected in tidal breathing conditions, aerosol is expelled to waste during the exhalation phase. Compared to general purpose nebulizers, which can nebulize different drugs, to avoid incorrect dosing of the medication, the eFlow® CS uses a unique ready-to-use unit-dose vial, designed to mitigate misuse and ensure dose uniformity.[3,52,54] The device requires to be disassembled and cleaned after each use to prevent clogging of the mesh openings. At the time of this review, the eFlow® system used for cystic fibrosis is being sold for $800–1,000.[51]

Traditional nebulization route has some limits indeed, especially in regard to the output variation between different nebulizers of the same type. In fact, factors affecting nebulizer output are inextricably linked with those affecting particle size and nebulization time.[55] Output can be diminished if the jet is blocked with dirt or drug crystals. Repeated uses may increase the diameter of the air orifice thus increasing the mean diameter of the droplets generated and reducing the air speed. This aging may be due to mechanical wear from the compressed air source or to excessive cleaning. Nebulizers designed to deliver small particles may have increased residual volume, decreasing drug output and increasing recirculation of the nebulizer solution, thus lengthening nebulization time. Increasing the volume fill improves drug output but lengthens nebulization time. Increasing driving gas flow rate may help, but for home use a higher performance compressor may be needed.[56] Another disadvantage is represented by the need of the end-user to load the medication prior to each administration.[57]

Despite some drawbacks associated with nebulizers, current evidence suggests that the efficacy of treatments administered to patients with moderate-to-severe COPD via nebulizers is similar to that observed with pMDIs and DPIs.[20–23] Furthermore, for some patients, the use of both a nebulizer as maintenance therapy and a handheld inhaler as rescue medication may provide the best combination of efficacy and convenience.

Pharmacology of glycopyrrolate via nebulizer

Chemistry and pharmacokinetics

Glycopyrronium, the active moiety of its bromide salt, also known as glycopyrrolate, is an antimuscarinic drug that was initially approved by the FDA for systemic administration for the reduction of sialorrhea due to preoperative stages, neuromuscular, and drug-related diseases[58,59] and due to the

property of reducing gastric secretions, as a treatment for peptic ulcer.[60] It is a quaternary ammonium derivative – (1,1-dimethylpyrrolidin-1-ium-3-yl) 2-cyclopentyl-2-hydroxy-2-phenylacetatethat[61] – with a peripheral effect similar to atropine. The chemical structure of GB is reported in Figure 2.

GB is rapidly absorbed into the systemic circulation after inhalation, ≈90% via lung and ≈10% via gastrointestinal absorption.[62] The mean terminal elimination half-life ($t_{1/2}$) of GB-DPI, is half that reported for GB-MDI (from 13 to 22 hours for a dose range of 25–200 µg[63] and from 6.3 to 9.6 hours for a dose range of 14.4–115.2 µg), leaving open discussion on whether these pharmacokinetic features should be interpreted as a signal favoring the once daily (OD) or a bis in die (BID) administration. During the Phase II study by Leaker et al,[41] a formulation of GBn delivered by the eFlow® nebulizer was rapidly absorbed with peak plasma concentrations within 15–30 minutes. There were only two measurable plasma GBn concentrations available with the 12.5 µg dose. Therefore, 12.5 µg was not included in the dose proportionality analysis. The elimination half-life ($t_{1/2}$) of GBn was calculated for the 0–1 and 0–12 hours intervals. The median $t_{1/2}$, 0−1 hours ranged from 1.10 to 1.15 hours, and median $t_{1/2}$, 0–12 hours ranged from 2.30 to 7.45 hours, following administration of 50, 100, 200, and 400 µg of GB, respectively.[41]

Metabolism and elimination

GB is nonenzymatically hydrolyzed to form the major circulating metabolite, M9, which is a racemic carboxylic acid derivative, formed from the swallowed fraction of inhaled GB (Figure 2).[62] In animal models, the primary biotransformation pathways for GB have been demonstrated to include the addition of one or two oxygen atoms to the cyclopentane and phenyl rings and dehydrogenation on the cyclopentane ring.[64] Further hydrolysis of the ester linkage forms the M9 metabolite. About 10% of systemic exposure is due to the swallowed drug, oral bioavailability of GB being 5%. The metabolite M9 has a plasma concentration that is approximately the same as that of the parent drug after inhalation but not after intravenous administration.[64] Biliary excretion contributes ~5% to total clearance. GB also forms various mono and bis-hydroxylated metabolites in vitro. Glucuronide and sulfate conjugates of GB were recovered in urine of subjects receiving multiple dosages of inhaled drug.[64] The most quantitatively important cytochrome that contributes to the metabolism of GB is CYP2D6.[64]

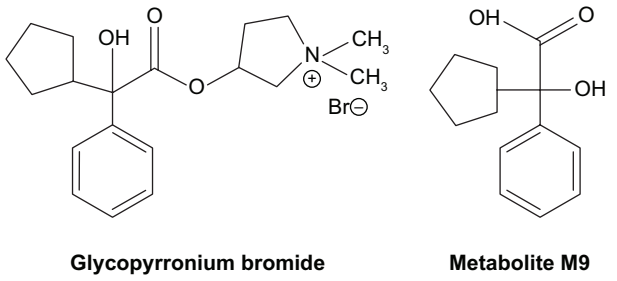

Figure 2 Chemical structure of glycopyrronium bromide (left) and its plasma metabolite M9 (right).
Note: M9 is formed through nonenzymatic hydrolysis of glycopyrronium bromide.

Pharmacodynamics

Muscarinic antagonists promote the relaxation of airway smooth muscle by blockade of the acetylcholine receptor.[65] GB is a competitive muscarinic receptor antagonist that bronchodilates the airways by inhibiting acetylcholine induced bronchoconstriction in bronchial smooth muscle cells.[66] The three main muscarinic receptors related with human lung bronchial dynamics are the M_1, M_2, and M_3 receptors. M_2 receptor protects against bronchoconstriction and its block may increase heart rate.[36,66] The bronchoconstrictor effect of acetylcholine is mediated mainly through M_3 receptors located on airway smooth muscle cells, whereas M_1 receptors enhance cholinergic reflexes. In contrast, M_2 receptors on cholinergic nerve endings inhibit acetylcholine release, thus reducing bronchoconstriction, and should not be blocked.[67] Mucus secretion is largely mediated by M_3 receptors and M_3 receptor blockade may also reduce mucus hypersecretion.[68,69] In vitro, GB binds with high affinity to all the bronchial muscarinic receptors but has four- to fivefold higher selectivity for human M_1 and M_3 receptors than for the human M_2 receptor (equilibrium binding affinity constants of 9.60–9.81 and 9.47–9.64 vs 8.70–9.25).[6,70] GB has also different dissociation kinetics for the three muscarinic receptors, with dissociation half-life of 11.4 and 13.9 for M_3 and M_1, respectively, vs 1.07 min for M_2 and kinetic off rate of 0.061 and 0.05 vs 0.646 per minute, respectively.[62,66] GB showed greater equilibrium binding selectivity (M_3 selectivity ratio [ratio of the affinity constant for the M_3 receptor vs that for the M_2 receptor] of 7.76-fold vs 2.09-fold) and kinetic selectivity (M_3 kinetic selectivity ratio [ratio of the area under the simulated association and dissociation curves for the M_3 receptor vs that for the M_2 receptor] of 11.41-fold vs 4.30-fold) for M_3 versus M_2 than tiotropium bromide, indicating the potential for an improved therapeutic index.[62,66]

Selective M_1 and M_3 receptors' blockers such as tiotropium and GB are therefore preferable to nonselective

muscarinic antagonists, such as atropine and ipratropium bromide, which express their effects also on the M_2 receptor subtype.[68,71] Both GB and tiotropium are in fact selective for M_1 and M_3 receptors and have a similar duration of action with slow dissociation for these receptor subtypes.[72] The slow dissociation profile of GB contributes to the long duration of action seen in clinical studies.[73] Accordingly, GB rapidly dissociates from M_2 receptors, thus avoiding their prolonged presynaptic blockade and reducing the antagonizing effect of acetylcholine release.[72,74]

Compared to tiotropium bromide, GB has a faster onset of action both in vitro and in vivo animal models.[70] In fact, GB has shown to have both lower equilibrium binding affinity constants and a faster kinetic off rate (9.59 and 0.061 vs 10.37 and 0.015 per minute, respectively), which justifies its faster onset of action also in patients with moderate-to-severe COPD when compared with tiotropium bromide at a dosage of 18 μg.[75] The onset of action, however, appeared slower both in terms of relief from airflow obstruction and in reduction of static hyperinflation when compared with aclidinium bromide 400 μg in a double-blind cross-over study in severe and very severe patients with COPD.[76]

GB has been shown to be more potent than ipratropium bromide and tiotropium bromide in terms of concentration drug necessary to inhibit the contractile bronchial smooth muscle response by 50%.[77] In a recent report that compared in vivo and in vitro effects of GB-DPI, aclidinium bromide DPI, and tiotropium bromide DPI, GB-DPI resulted to be the most potent of the three LAMAs investigated, inducing, with aclidinium, a faster bronchodilation compared to tiotropium.[78] However, given the fact that so far, the approved marketed doses are not isoeffective for the two LAMAs, to make precise pharmacodynamics speculations of their effect in vivo remains a difficult task. A potential disadvantage brought by the GB fixed-dose combinations currently available on the market is represented by the GB dosage (≤50 μg); in fact, from the analysis of the forced expiratory volume in the first second (FEV_1) dose–response in pharmacodynamic studies, the optimal dose of GB appeared to be at least 100 μg, to be reflected in a FEV_1 difference of >100 mL.[11]

Glycopyrrolate-approved formulations

GB has been initially approved by the European Medicines Agency[79] and the Pharmaceuticals and Medical Devices Agency[80] in 2012 and by the FDA[81] in 2015, as a standalone treatment for COPD as a dry-powder inhalation formulation. Subsequently, while in Europe it has been approved with OD posology, FDA approved its usage as BID long-acting bronchodilator both as a standalone treatment and as a fixed-dose DPI combination with indacaterol. An MDI formulation containing a fixed-dose combination of GB and formoterol fumarate has been available in USA and Japan since 2016. A DPI formulation containing a triple combination of GB, formoterol fumarate, and beclomethasone has been approved for marketing in EU in May 2017.[82]

At the time of the present review, a nebulized formulation of GB is awaiting approval from FDA as a maintenance treatment for patients with COPD.[83]

Efficacy studies

Phase II and Phase III efficacy and safety clinical trials involving GBn are summarized in Table 2.

Phase II studies

GBn was studied in a Phase II, two-center, randomized, placebo-controlled, double-blind, dose ranging, single-dose, six-way cross-over trial in 35 patients with moderate-to-severe COPD (GOLD II/III), aged 40–75 years.[41] All patients were required to have at least 12% and 150 mL reversibility to inhaled ipratropium bromide as inclusion criteria. Eligible patients were randomized to receive a single dose of GBn via eFlow® nebulizer (12.5, 25, 50, 100, and 200 μg) or placebo in six treatment visits separated by washout periods of 5–12 days; each dose was followed by an onset of response on placebo-adjusted FEV_1 in <5 minutes (60, 80, 100, 130, and 140 mL). The bronchodilating effect progressively decreased over 24 hours period with a dose–response relationship, so that the higher the initial dose, the longer the duration of bronchodilation. The placebo-adjusted FEV_1 improvement at 24 h postdose was >100 mL with both the 100 μg (104 mL increase over placebo effect) and 200 μg (118 mL increase) doses; only the latter doses produced a significant improvement over placebo.[41]

The eFlow® was able to deliver all doses of GBn in <2 minutes (range 1.6−1.9 minutes). GBn peak plasma concentrations were measured within 15–30 minutes.[41]

The GOLDEN-1 study was a Phase II, multicenter, randomized, double-blind, placebo-controlled, four-period, incomplete block, cross-over study.[42] The primary outcomes were the mean change in 24-hour postdose trough FEV_1, and the standardized change in FEV_1 area under the curve (AUC) (0–12 and 12–24 hours) on days 1 and 7.[42] Secondary outcome measures were peak FEV_1 (maximum FEV_1 during the first 4 hours postdose on days 1 and 7); time to onset of action (time necessary to obtain a ≥10% improvement in postdose FEV_1); treatment responders (proportion of subjects

Table 2 Available studies on nebulized GB for COPD treatment

Name (ID)	Study design	Drugs	Population	Primary endpoints	Main secondary endpoints	Main results
Leaker et al[41]	Phase II, two-center, randomized, placebo-controlled, double-blind, dose ranging, single dose, six way cross-over	GBn via eFlow® nebulizer, single dose (12.5, 25, 50, 100, and 200 μg)	42 (40–75 years of age with moderate-to-severe COPD)	– Dose ranging	– AE, vital signs, ECG and clinical laboratory tests – Plasma pharmacokinetic of GBn	– Dose–response relationship for time normalized FEV_1 (0–24 hours) and placebo-adjusted mean ΔFEV_1 ($P<0.05$ with GBn 50 μg) – Clinically meaningful improvements (>100 mL) for 100 and 200 μg doses – Comparable AE profile to placebo – Peak plasma concentration at 15–30 min – Dose-proportional increase in C_{max} – $t_{1/2}$ 0–1 hours: 1.10–1.15 hours – $t_{1/2}$ 0–12 hours: 2.30–7.45 hours for GBn 50–400 μg
GOLDEN-1,[42] NCT01426009	Phase II, multicenter, randomized, double-blind, placebo-controlled, seven arm, four-period cross-over, incomplete block design, 1 week	– GBn via eFlow® nebulizer OD – Tiotropium bromide via HandiHaler® OD – Ipratropium bromide via general purpose nebulizer 500 μg TID	105 (40–75 years of age with moderate-to-severe COPD)	– Trough FEV_1 – Mean change in 24-h postdose trough FEV_1 on days 1 and 7 – FEV_1 AUC – Standardized change in FEV_1 AUC (0–12 and 12–24 hours) on days 1 and 7	– Proportion of subjects reaching MCID in trough FEV_1 on days 1 and 7 – Safety and tolerability of GBn – AEs, vital signs, ECG, and clinical laboratory tests – Rescue medication use	– No difference in AEs between dosages – No dose relationship for AEs – Vital signs and ECG comparable between treatment groups – Significant dose-related improvements in FEV_1 (AUC 0–24) vs placebo (110–169 mL)
GOLDEN-2,[43,86] NCT01706536	Phase II, randomized, double-blind, placebo-controlled, parallel arm, 4 weeks	– GBn via eFlow® nebulizer BID (12.5, 25, 50, and 100 μg) – Aclidinium bromide via Pressair® 400 μg	282 (35–75 years of age, with moderate-to-severe COPD)	– Morning trough FEV_1 on 29th day	– FEV_1 AUC (0–12) – FEV_1 AUC (12–24) – Peak FEV_1 – TEAE leading or not to discontinuation – Treatment-emergent SAE	GOLDEN-2 + GOLDEN-6 pooled (N=378): – Clinical important improvements vs placebo at days 7 and 28 (82 mL for GBn 6.25 BID and 177 mL for 100 μg BID) – Corresponding FEV_1 AUC (0–12): from 84 to 183 mL
GOLDEN-6,[47,86] NCT02038829	Phase II, randomized, double-blind, placebo- and active-controlled, cross-over, 1 week	– GBn via eFlow® nebulizer BID (3, 6.25, 12.5, 25, and 50 μg) – Aclidinium bromide via Pressair® 400 μg BID	96 (40–75 years of age with moderate-to-severe COPD)	– Change in trough FEV_1 day 7	– FEV_1 AUC (0–12 hours) – TEAE (overall and by treatment)	– GBn doses of 25 and 50 μg comparable to aclidinium – GBn 3 μg dose = no effect dose
GOLDEN-3,[44,88,92] NCT02347761	Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter, 12 weeks	– GBn via eFlow® nebulizer BID (25 and 50 μg)	653 (40–75 years of age with moderate-to-severe COPD)	– Trough FEV_1 at week 12	– FEV_1 AUC (0–12) at 12 weeks in the sub-study population – Trough FVC at week 12 – SGRQ at week 12 – Rescue medication use – TEAE leading or not to discontinuation – N treatment emergent SAE – MACE	GOLDEN-3 and GOLDEN-4 pooled analysis: Trough FEV_1 vs placebo at week 12 for GBn 25 and 50 μg (all $P<0.0001$): – GOLDEN-3: 0.105 and 0.126 L; – GOLDEN-4: 0.084 and 0.082 L; No difference in efficacy depending on previous chronic treatment Trough FVC_1 vs placebo at week 12 for GBn 25 and 50 μg (all $P<0.0001$):

GOLDEN-4,[45,88,92] NCT02347774	Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter, 12 weeks	– GBn via eFlow® nebulizer BID (25 and 50 μg)	640 (40–75 years of age with moderate-to-severe COPD)	– Trough FEV_1 at week 12	– Trough FVC – SGRQ – Rescue medication use – TEAE leading or not to discontinuation – Treatment emergent SAE – MACE	– GOLDEN-3: 0.149 and 0.167 L – GOLDEN-4: 0.130 and 0.113 L SGRQ week 12: Placebo-adjusted LS mean (SD) – GBn 25 μg: −3.35 (0.79) – GBn 50 μg: −2.71 (0.80) Adjusted LS mean (SD) symptoms domain: – GBn 25 μg: −3.61 (1.16) – GBn 50 μg: −3.92 (1.16) SGRQ responders: – 46.8, 41.7, and 34.5% for 25 and 50 μg and placebo ($P<0.05$) Most frequent TEAEs: COPD worsening and cough. No difference in exacerbation rates vs placebo TEAEs leading to discontinuation more frequent for placebo (9% in both studies) GOLDEN-3: 3 MACE (GBn 50 μg) GOLDEN-4: 2 MACE (placebo) No difference in ECG parameters
GOLDEN-5,[46,89] NCT02276222	Phase III, randomized, open-label, active-controlled, parallel-group, multicenter, long-term, 48 weeks	– GBn via eFlow® nebulizer 50 μg BID – Tiotropium bromide via Handihaler® 18 μg OD	1,086 (GBn n=620, tiotropium n=466) (40–75 years of age with moderate-to-severe COPD)	– TEAEs – Treatment-emergent SAEs – TEAEs leading to discontinuation	– MACE, including cardiovascular death, ischemia/infarction, and stroke – Trough FEV_1 at 48 weeks	SGRQ responders were similar for tiotropium (48.6%) and GBn (51.2%) at week 24 TEAEs similar for GBn (69%) vs TIO (67%) Most frequent TEAEs: COPD and cough TEAEs leading to discontinuation: 10% for GBn and 2.8% for TIO Most frequent for GBn: cough (2.3%); dyspnea (1.5%); and COPD (1.9%) MACE incidence rate: 6.4/1,000 persons per year for GBn and 20.3/1,000 per year for TIO Three deaths in GBn group and four deaths in TIO No deaths treatment related

Note: ID, ClinicalTrials.gov identifier.

Abbreviations: AEs, adverse events; BID, bis in die; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GBn, nebulized glycopyrronium bromide; GOLDEN, Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer; LS, least squares; MACE, major adverse cardiovascular events; OD, once daily; MCID, minimal clinical importance difference; QTc, corrected QT interval; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire; TEAE, treatment-emergent adverse event; TID, ter in die.

with clinically meaningful change from predose in trough FEV_1 on days 1 and 7); and safety and tolerability.[42]

A total of 140 patients with moderate-to-severe COPD were randomized to four of seven treatments: GBn (25, 50, 100, and 200 µg) or placebo OD via eFlow® nebulizer, open-label tiotropium 18 µg OD and open-label ipratropium 500 µg three times a day delivered via jet nebulizer. All doses of GBn demonstrated dose-related and significant improvements in FEV_1 AUC (0–24 hours) on day 7 compared to placebo, with estimated differences between GBn doses and placebo ranging between 110 and 169 mL.[84]

Following the pharmacokinetic profile of GBn, in the subsequent Phase II studies, only the BID posology has been maintained.

Two randomized, double-blind, placebo- and active-controlled Phase II studies, GOLDEN-2[43,85] and GOLDEN-6,[47] further characterized the efficacy of GBn in terms of dose–response relationship recruiting a total of 378 patients with moderate-to-severe COPD (GOLDEN-2, N=282; GOLDEN-6, N=96). The GOLDEN-2 study had a parallel group design of 28 days, while the GOLDEN-6 was a 7-day cross-over trial. It should be underlined that for the GOLDEN-2 study eligible patients were <40 years old.[47]

The primary endpoint of both studies was the change from baseline in trough FEV_1 on day 7 or day 28. Safety and tolerability were evaluated based on the incidence of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and discontinuations due to TEAEs. FEV_1 AUC 0–12 was a secondary endpoint. The data were pooled for the lung function assessments, common to both studies.[31,47]

In both studies, increasing doses of GBn (3–100 µg BID via eFlow® CS nebulizer) were compared with placebo or aclidinium bromide 400 µg BID (Tudorza® Pressair®). GBn produced rapid onset (≤5 minutes) dose-related bronchodilation following a single-dose administration. Improvements were maintained over a 24-hour period at all doses >50 µg.[41,47] The primary endpoints of both studies were reached obtaining on days 7 and 28 a significant improvement of the placebo-adjusted trough FEV_1, with dose-related improvements ranging from 82 mL for the 6.25 µg dose to 177 mL for 100 µg BID, with corresponding changes in FEV_1 $AUC_{0–12}$, ranging from 84 to 183 mL. The improvements in lung function for the 25 and 50 µg BID doses were comparable to those obtained with aclidinium bromide (trough FEV_1 =157 mL, FEV_1 $AUC_{0–12}$ =190 mL). The GBn dose of 3 µg BID was identified as the "no-effect" dose.[43,46,86]

The GOLDEN-2 and GOLDEN-6 dose-finding studies supported the selection of GBn 25 and 50 µg BID doses to advance in the subsequent Phase III GOLDEN trials.[43,45,86]

Phase III studies

GOLDEN-3[44] and GOLDEN-4[45] were twin Phase III, 12 weeks, randomized, double-blind, placebo-controlled, parallel-group, multicenter, efficacy, and safety trials.

The primary endpoint was change from baseline at week 12 in trough FEV_1. Key secondary endpoints included forced vital capacity (FVC), St George's Respiratory Questionnaire (SGRQ), and rescue medication use. Safety was also assessed throughout the study.

Included patients were 40–75 years old, with a ≥10 pack-year smoking history and a moderate-to-very-severe COPD (postbronchodilator FEV_1 <80% of predicted normal or FEV_1/FVC ratio <0.70). To include a closer-to-real-life COPD population, patients with maintenance treatment with LABA (31%) and ICS (29%) and co-existing cardiovascular disease were not excluded in both studies; patients were stratified by cardiovascular history, 64% being at high risk.[87] The administration of both doses of GBn/eFlow® (25 and 50 µg BID) resulted in statistically and clinically significant improvements compared to baseline in placebo-adjusted trough FEV_1 (GOLDEN-3: +105 and +126 mL; $P \leq 0.0001$; GOLDEN-4: +84 and +82 mL; $P \leq 0.0001$) and placebo-adjusted trough FVC (GOLDEN-3: +149 and +167 mL, $P < 0.001$; GOLDEN-4: +130 and +113 mL, $P < 0.01$) at week 12.[87,88]

GOLDEN-5 study was a Phase III, randomized, open-label, active-controlled, parallel-group, multicenter, long-term safety trial of 48 weeks of treatment with GBn delivered by the eFlow® CS system or tiotropium 18 µg OD in 1,087 moderate-to-very-severe COPD patients.[46] The population included patients with background use of LABA and history of significant cardiovascular disease.[46]

The primary endpoints were the incidence of TEAEs, SAEs, and discontinuations due to TEAEs. Secondary endpoints included patient-reported outcomes, rescue medication use, and the mean change from baseline over 48 weeks in trough FEV_1. Lung function results confirmed the findings from GOLDEN-3 and -4 studies. Considering patients with and without background LABA therapy, improvements in trough FEV_1 after GBn administration were not different, 99 and 105 mL, respectively.[46,89]

GOLDEN-7 is a Phase I randomized, open-label, single-dose per dosing period, five-way cross-over study in subjects aged 40–70 years with a diagnosis of moderate-to-severe COPD designed to evaluate the total systemic exposure and lung bioavailability of GBn compared to GB delivered by Breezhaler® (Seebri®). GB was administered with and without activated charcoal. Unfortunately to date, no results are available for this study, as the available abstracts have been withdrawn.[47,90]

Safety and tolerability

During the Phase II trial conducted by Leaker et al, single doses of GBn were well tolerated with AE profiles comparable to placebo. After all dosages, there were no clinically relevant changes in vital signs and ECG parameters, including QTc, and no typical muscarinic side effects, such as dry mouth and increased heart rate.[41]

In the GOLDEN-1, all doses of GBn were well tolerated with similar AE rates between placebo and GBn (31.2, 29.7, 26.9, 35.5, and 30.7% for placebo, 25, 50, 100, and 200 µg, respectively). There was no apparent dose–response relationship for incidence and severity of AEs. Mean changes in vital signs and ECG parameters from baseline to day 7 were comparable between the treatment groups.[41] No clinically significant differences compared to placebo were observed in terms of heart rate, blood pressure, and ECG parameters.[42] The GBn safety profile was similar to placebo, tiotropium, and ipratropium in regard to cardiovascular AEs.[91]

GBn was well tolerated in GOLDEN-3 and -4 trials, with a combined overall incidence of TEAEs being numerically lower with GBn 25 and 50 µg BID doses compared to placebo (43.4, 50.7, and 52.3% for GBn 25 and 50 µg doses and placebo, respectively). The most frequent AEs were represented by skin injury, headache, acute COPD exacerbations, cough, and dyspnea. Discontinuations due to TEAEs were numerically higher in the placebo group. There was one cardiovascular-related death in the 50 µg BID group.[88]

A safety analysis of the 48 week GOLDEN-5 trial, in which the primary objectives were the number and percentage of patients with TEAE, demonstrated comparable and consistent results with GOLDEN-3 and GOLDEN-4 trials at 12 weeks.[46,89] Discontinuation rate was 10% for GBn and 2.8% in patients receiving tiotropium; the most frequent TEAEs leading to discontinuation for GBn were cough (2.3%), dyspnea (1.5%), and COPD (1.9%). The incidence rate of major adverse cardiovascular events (MACE) was 6.4 per thousand person-years for GBn and 20.3 for tiotropium.[89] There were seven deaths during the study, none of which were considered treatment related: three in the GBn group (0.5%) and four in the tiotropium group (0.9%).[89] Results from GOLDEN-5 trial, focused on long-term safety of GBn compared to placebo, showed that GBn BID was well tolerated, with a similar overall incidence of adverse events compared to the standard of care (48.6% for patients treated with GBn and 51.2% for tiotropium).[89] Compared to tiotropium, the incidence of MACE was lower in the GBn group, although not significantly different compared to patients treated with tiotropium (6.4/1,000 persons per year for GBn and 20.3/1,000 per year for tiotropium), finding consistent with results from the GOLDEN-2 trial.[85] The pooled analysis of GOLDEN-3 and -4 trials demonstrated a very low incidence of anticholinergic-related events such as dry mouth, with an incidence ranging between 0.5 and 2.3% in patients treated with GBn; only one gastrointestinal obstruction was reported in both studies, while glaucoma-related adverse events were very rarely observed (0.5 and 0.2% for GBn 25 and 50 µg doses, respectively).[88] As for urinary tract adverse events, urinary tract infection was reported in 2.3 and 1.9% for the GBn 25 µg dose and 3.2 and 2.3% for the highest dose across the GOLDEN-3 and -4 trials, respectively. Urinary retention was not observed throughout the studies.

Quality of life, patient satisfaction, and acceptability

Pooled data including respiratory symptoms from GOLDEN-3 and -4 studies (1,293 patients in total) and data from the long-term trial GOLDEN-5 (1,086 patients) were analyzed. Patients had the same inclusion criteria across all trials.[87–89]

Clinically meaningful changes (≤4.0 unit reduction) in SGRQ scores at week 12 were observed in 46.8, 41.7, and 34.5% of patients treated with GBn 25 and 50 µg BID dosages and placebo, respectively. Improvements were largely driven by changes in the SGRQ symptom domain.[87] During GOLDEN-5, administration of GBn 25 and 50 µg BID resulted in statistically significant improvements from baseline in health-related quality of life, using the Evaluating Respiratory Symptoms in COPD (E-RS™: COPD) electronic diary. E-RS™: COPD total score was collected starting from week 2 ($P<0.05$ vs placebo for both doses), with no significant effect on rescue medication use. E-RS responders at week 12 were 48.1, 40.3, and 36.9% of patients in the GBn 25 µg, 50 µg, and placebo groups, respectively; the placebo group scored −0.6 from the baseline while GBn −1.76 and −1.52 for doses of 25 and 50 µg, respectively. In GOLDEN-5, improvements in E-RS total scores were seen across all visits in the GBn and tiotropium groups, with similar changes in the score (from −1.30 to −1.86 on the baseline score at week 12 and −1.5 for both tiotropium and GBn at week 48).[92]

A survey conducted among patients participating in the GOLDEN-5 study, which collected 473 questionnaires about patient-reported satisfaction with the investigational nebulizer and the ability to use it, suggested that regardless of previous nebulizer use, 75% of patients were "satisfied" or "very satisfied" with the novel delivery system. A total of 83% of patients also reported being "confident" to "very confident" that the study drug was being efficiently delivered to their lungs by the eFlow® CS nebulizer. Additionally, >70% of

the patients also rated the investigational nebulizer as "easy" or "very easy" to assemble, operate and clean.[93]

Conclusion and place in therapy

The number of elderly patients with COPD will increase as we become more efficient treating the disease and their chronic morbidities. It is not uncommon during everyday clinical practice to be unable to prescribe an adequate inhalation therapy for an elderly COPD patient due to his inability to handle the device or his low adherence to the suggested treatment. Treatment options that do not require coordination for activation and inhalation or necessitate an inspiratory peak flow threshold to be activated should represent the best treatment option for these patients. Nebulizers seem to fulfill that missing spot, although no nebulized bronchodilators are currently available for the treatment of stable COPD. The use of high efficiency nebulizers may bring together the highest number of advantages and the lowest number of disadvantages in terms of treatment efficacy and tolerability. GBn might be the first nebulized LAMA to be approved for use in COPD patients. The eFlow® CS nebulizer has also some limits that should be considered: it is expensive and its maintenance may be complicated due to the need of cleaning the device after each administration. The latter aspect should not be forgotten, especially in patients that may be a priori selected for their inability to handle properly traditional inhalation devices.

The pathophysiology and functional impairment in patients with COPD guides the current technology dedicated to bronchodilator delivery, which should strive to assure the best efficiency of drug deposition within the lung, obtained with the lowest chance of critical errors possible. Nebulized glycopyrronium may represent the starting point of an alternative tool to increase the efficiency of long term bronchodilator therapy, especially in patients who present issues with the employment of devices containing predosed drugs.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

PS has received financial support for research from Pfizer, Almirall, Chiesi Farmaceutici, and AirLiquide. He has received honoraria for lectures at national meetings from Chiesi Farmaceutici, Novartis, Zambon Italia, AstraZeneca, Almirall, GlaxoSmithKline, Boehringer Ingelheim, Menarini, and Malesci-Guidotti. He has served as consultant for Zambon Italia, AstraZeneca, Novartis, Chiesi Farmaceutici, and Boehringer Ingelheim. DR has received honoraria for lectures from Astra Zeneca and Boehringer Ingelheim. AC, VV, and MR report no conflicts of interest in this work.

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