COPD PATIENTS' NEEDS AND CURRENT TREATMENT OPTIONS

Summary of Presentations from a Novartis-Supported Satellite Symposium, held at the 24th ERS Congress, Munich, Germany, on 8th September 2014

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MEETING SUMMARY

The objective of this meeting was to review the complexities surrounding the management and treatment options for different populations of chronic obstructive pulmonary disease (COPD) patients. Bartolome Celli chaired the symposium and outlined some of the current challenges for COPD management. Donald Tashkin discussed clinical assessment of the newly-diagnosed COPD patient, before moving on to review the initial pharmacotherapy options that are available, specifically the long-acting beta or muscarinic agonists. Claus Vogelmeier presented the options for COPD patients who remain symptomatic despite initial treatment, using data from clinical trials such as SPARK to compare different treatment approaches, and Jadwiga Wedzicha focused on higher-risk patients, presenting pertinent data from studies on patients with increased rates of COPD exacerbation. Finally, Bartolome Celli summarised the meeting and provided his expert insight on classifying COPD patients into phenotypic groups.

Welcome and Introduction

Professor Bartolome Celli

In terms of global disease burden, chronic obstructive pulmonary disease (COPD) is associated with 3,659,000 disability-adjusted life years, secondary only to ischaemic heart disease. COPD is also the cause of 154,000 deaths annually, and of 1,913,000 years of life lost.[1] The scale of the challenges within the COPD field is reflected by the active research interest in the field. Over the past 40 years there has been a noted increased interest in COPD with much investigative research and numerous associated publications being produced.

One important current issue that remains within the field is the level of cigarette smoking. Although this is a global issue of epidemic proportions, effective steps can be taken to reduce the proportion of people smoking. This was shown in New York City, where action from advocacy groups and education initiatives has resulted in the percentage of individuals who smoke dropping from an average of 22% in the 1990s to 14% in 2010. This action included tax increases on a local, state, and federal level, free patch programmes, smoke-free workplaces, and media campaigns.[2] Death resulting from smoking and COPD is, however, a problem across the world, and it is important to remember that COPD is not just related to lung disease and airflow; body-mass index, airflow obstruction, dyspnoea, and exercise capacity all contribute to risk of death.[3]

Since COPD is a multi-dimensional disease, the GOLD (Global initiative for chronic Obstructive Lung Disease) assessment tool[4] provides an easy-to-interpret classification system. This assessment tool takes into account the severity of airflow obstruction, symptoms, and exacerbations in order to provide an A/B/C/D classification of disease severity.[4] GOLD shows that in approaching COPD, a healthy lifestyle, smoking cessation, and environmental control are important, exercise and rehabilitation should be performed, and oxygen therapy should be administered.

A pulmonologist has multiple factors to consider when treating a patient with COPD, and has several treatment options and pathways available. The most appropriate therapeutic approach can differ depending on whether the patient is newly diagnosed, is still exhibiting symptoms despite monotherapy or even dual combination therapy, or if the patient is in a high-risk group.

Treating the Newly Diagnosed COPD Patient

Professor Donald Tashkin

It is important to note that newly diagnosed COPD patients may, in fact, have any level of severity of COPD, and therefore should have their level of severity assessed, ideally through a system such as GOLD since it provides a useful guide for initiating pharmacotherapy. In terms of the proportions of patients with mild-to-moderate disease, a study of the UK General Practice Research database classified patients according to the GOLD spirometric grade at time of diagnosis, and found that nearly 50% of patients were at GOLD Grade 2.[5]

An important challenge in COPD is under-diagnosis. Many physicians often rely on symptoms in order to make a diagnosis due to a lack of spirometers in their practice. While symptoms remain an important factor in the diagnostic process, the PLATINO study has evidenced that symptoms alone are insufficient to establish an accurate diagnosis; patients exhibiting shortness of breath, wheezing, cough, and phlegm were very infrequently diagnosed with COPD when spirometry was performed, highlighting the importance of this technique.[6]

Evidencing the challenge of under-diagnosis, it is estimated that COPD is undetected in ~50% of cases,[7] and in addition, COPD is misdiagnosed as asthma in ~23% of cases.[6] These factors mean that by the time a correct diagnosis has been made, up to half of the patient's lung function may have been lost[8] and the opportunity to impact the rate of progression by treating early has been missed. The loss of lung function is accelerated during the early stages of COPD, which provides an opportunity to intervene early and modify disease progression.[9] Early intervention through smoking cessation has been shown to significantly reduce both lung function decline and all-cause mortality in patients with mild-to-moderate airflow limitation,[10] further supporting the need for early intervention.

Once a correct diagnosis has been made, and lifestyle interventions have been considered, therapeutic approaches are important in

the management of COPD. In terms of pharmacotherapy, patients in GOLD category B should be treated with the long-acting beta agonists (LABAs) or long-acting muscarinic antagonists (LAMAs; also known as long-acting anticholinergics), which are bronchodilators that relax the muscles in the airways, decreasing resistance and improving FEV_1.[4,11,12] The 2014 GOLD guidelines recommend the LABAs formoterol, indacaterol, and salmeterol, and the LAMAs aclidinium bromide, glycopyrronium bromide, and tiotropium for inhalation. While there are few head-to-head studies of these drugs, indacaterol and tiotropium have been shown to significantly improve FEV_1 when compared to placebo.[13,14]

There have been several trials examining the effect of bronchodilators on patient outcomes. The UPLIFT trial demonstrated marked improvement in FEV_1 over 4 years in maintenance-naïve patients treated with tiotropium, showing that early intervention had a desirable outcome.[15] Similar improvements were also seen with the LAMA glycopyrronium in the GLOW1 and GLOW2 (Figure 1) trials.[15,16] Data from the INTENSITY trial show that LABA or LAMA monotherapy can improve patient-reported outcomes, which are important goals for COPD management.[17] These therapies improve exercise tolerance, health-related quality of life (QoL), reduce mortality and exacerbations, and also slow disease progression. A LABA/LAMA combination also presents a potential option for improving lung function and health status in maintenance-naïve patients; however, it is unclear which patients would most benefit from starting treatment on this combination compared to monotherapy.

Early treatment is important not only because this causes a symptomatic improvement in the QoL of patients, but it also provides an opportunity to slow the accelerated rate of the decline in lung function that is greatest in the early stages of COPD.

- Improvements in FEV_1 $AUC_{0\text{-}4h}$ were statistically significant with glycopyrronium vs placebo and tiotropium at Day 1 and Week 26, and comparable to tiotropium at Weeks 12 and 52

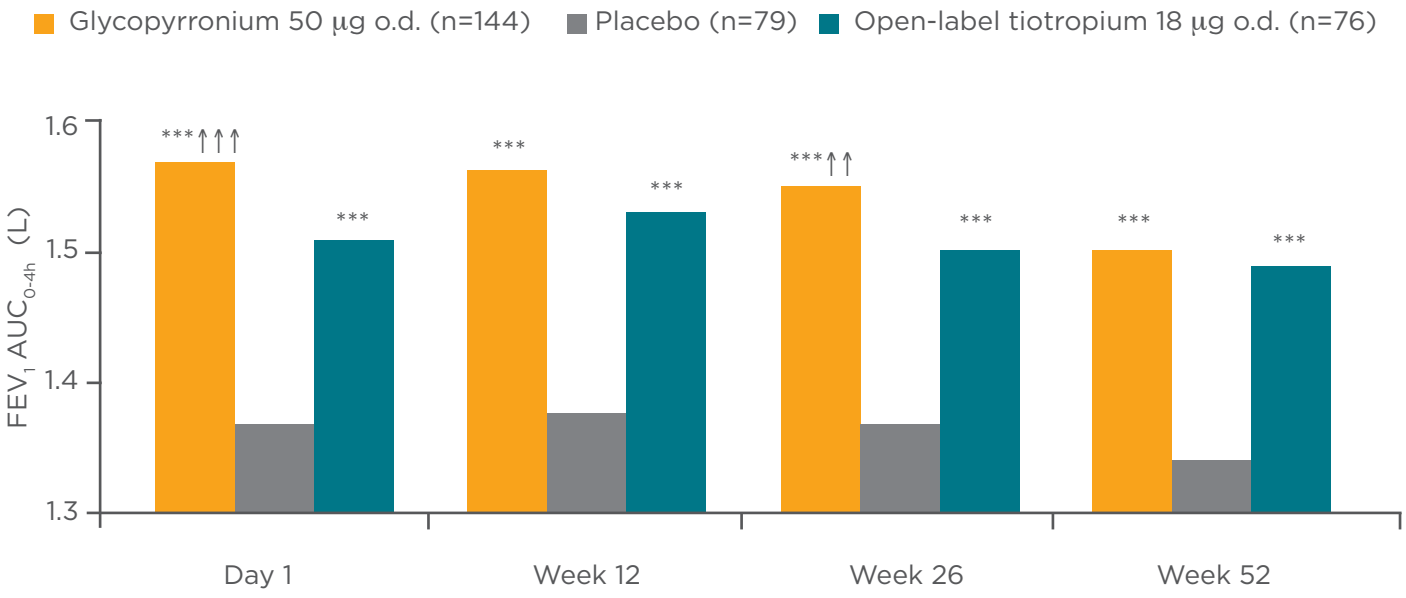


Figure 1: Glycopyrronium and tiotropium significantly improved FEV_1 versus placebo and tiotropium in the GLOW2 trial.

*Based on FEV_1, $AUC_{0\text{-}4h}$ following dosing between 08:00 and 11:00.

***p<0.001, versus placebo;↑↑↑p<0.001, ↑↑p<0.01; glycopyrronium versus open-label tiotropium.

Data are least-squares mean from subset of patients who underwent serial spirometry.

FEV_1: forced expiratory volume in 1 second; AUC: area under the curve; o.d.: once daily.

Adapted from Kerwin E et al.[16]

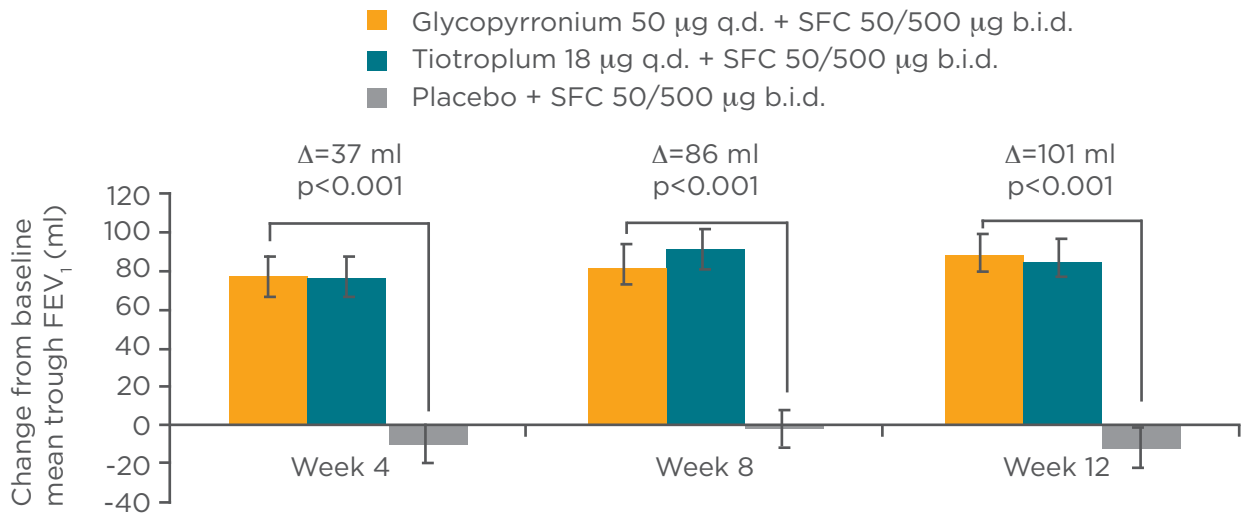


Figure 2: The addition of a LAMA to the LABA/ICS combination improves FEV_1 compared to placebo in the GLISTEN trial.

The primary objective of the study was met (non-inferiority of glycopyrronium 50 µg q.d. versus tiotropium 18 µg for trough FEV_1 after 12 weeks).

Data are least-squares mean±SE.

LAMA: long-acting muscarinic antagonists; LABA: long-acting beta agonists; ICS: inhaled corticosteroid; FEV_1: forced expiratory volume in 1 second; b.i.d.: bis in die (twice a day); SFC: salmeterol/fluticasone propionate; q.d.: quaque die (once daily); SE: standard error.

Adapted from Frith P et al.[34]

Options for COPD Patients who Remain Symptomatic Despite Treatment

Professor Claus Vogelmeier

Considering therapeutic options for those patients who remain symptomatic despite treatment, a patient in GOLD category D, with FEV_1 of 20% and severe emphysema, could potentially be given a LABA/LAMA combination, an inhaled corticosteroid (ICS)/LABA combination, or even an ICS/LABA/LAMA triple combination. LABA/LAMA combinations are suggested for treatment since they have distinct mechanisms of action, and target both the peripheral and central airways.[18]

There is clinical evidence supporting the LABA/LAMA combination, such as the SPARK trial[19] which included very ill patients who had severe or very severe disease and a history of at least one exacerbation; patients receiving QVA149 (indacaterol + glycopyrronium) had consistent and significant improvements in QoL over the 64-week study when compared to glycopyrronium or tiotropium alone. The BLAZE trial,[20] which reported patient outcomes, used a three-period cross-over design. Patients receiving QVA149 had significantly improved transition dyspnoea index (TDI) scores compared to both placebo and tiotropium (0.88 versus -0.49 and 0.39).[20] In terms of head-to-head comparisons of other LABA + LAMA, the QUANTIFY study[21] showed that QVA149 was superior to tiotropium + formoterol for the clinically-relevant endpoint of percentage TDI responders.

There are various choices to make when initiating treatment, and the choice to give monotherapy or combination therapy depends on a number of factors, including whether the patient is newly diagnosed, therapy naïve, or is symptomatic and has exacerbations. A combination of LABA with an anti-inflammatory such as an ICS is more effective than the individual drugs;[22-29] however, no combination treatment has been shown to have a mortality benefit.[22] A problem with ICS treatment, however, is the side-effect profile, the most relevant being the risk of developing pneumonia.[30,31] When considering whether to treat with an ICS, the correct patient type must therefore be selected. The ILLUMINATE trial[32] made it clear that an ICS/LABA combination does not make therapeutic sense for patients with no exacerbation history; patients receiving the LABA/LAMA combination QVA149 had improved TDI scores at both Week

12 and 26 versus the ICS/LABA combination of salmeterol and fluticasone (treatment differences: 0.59 and 0.76). However, despite recommendations, more than one-third of patients in GOLD groups A and B are receiving ICS.[33]

Patients on dual combination therapy showing a continued lack of disease control may require the addition of further medication in order to improve outcomes. The GLISTEN trial (Figure 2) examined the effects of glycopyrronium, tiotropium, or placebo all in combination with salmeterol + fluticasone over 12 weeks. The addition of either LAMA to LABA/ICS improved FEV_1 and QoL compared to placebo, demonstrating that patients who are symptomatic on ICS/LABA may benefit from the addition of a LAMA such as glycopyrronium or tiotropium.[34] A systematic review of four trials determined that ICS withdrawal did not result in an increase in exacerbations.[35] The recently published large WISDOM trial also demonstrated that removing ICS from patients on triple therapy did not lead to significant increases in exacerbation rate, regardless of patient subgroup.[36]

Maintenance therapy with a LABA or LAMA may improve symptoms, but if symptoms persist there are a number of options to consider. A choice must be made whether to treat with a LABA/LAMA or, if the patient has frequent exacerbations, LABA/ICS combination, or with triple therapy. These options depend on the status of the patient and their level of exacerbation risk.

Managing Higher Risk COPD Patients

Professor Jadwiga Wedzicha

The real value of GOLD is that it helps to understand risk and also informs on how to prevent it. Exacerbation risk is complex, and comorbidities are intertwined with this risk; patients who have one exacerbation per year may have heart failure or other issues that increase their risk. Patients in GOLD group B have been shown to have poorer survival rate than those in group C.[37] Overall, 22% of patients with moderate disease (GOLD Stage 2) have two or more exacerbations per year, and since approximately 70% of COPD is in Stage 2, this results in a large amount of morbidity due to exacerbation.[38]

COPD exacerbations can be triggered by bacteria, viruses, and pollutants, resulting in inflamed airways and leading to a number of effects, including: systemic inflammation, bronchoconstriction, oedema and mucous, expiratory flow limitation, and dynamic hyperinflation.[39] Most exacerbations improve in 7–10 days but some persist, and approximately 25% of exacerbations do not recover to a normal state after 5 weeks;[40] this may be due to the persistence over hyperinflation post-exacerbation. More persistent exacerbations have been observed in patients with airway infections,[41] and hospitalisation for COPD is associated with a significant risk of death.[42]

The INSPIRE study showed that exacerbation rates were similar in patients treated with tiotropium or salmeterol + fluticasone.[43] A study that followed on from this was SPARK,[19] which investigated exacerbations in patients treated with QVA149 (indacaterol + glycopyrronium), glycopyrronium alone, or open-label tiotropium alone. All patients had at least one exacerbation in the previous year, and their mean FEV_1 was 37.2% predicted. QVA149 significantly improved mean trough FEV_1 compared to the other two groups over the course of the 64-week study, reduced moderate and severe COPD exacerbations by 12% versus glycopyrronium (primary endpoint; p=0.038) and 10% versus open-label tiotropium (secondary endpoint; p=0.096) (Figure 3), and reduced the annualised rate of total and mild exacerbations. This reduction in rates was associated with improvements in health status over the course of the study. Patients receiving QVA149 self-reported changes from baseline of -0.37 and -0.44 in daily symptoms scores ($p<0.01$) and of -0.09 and -0.13 in dyspnoea scores ($p\leq0.0001$) versus glycopyrronium or tiotropium alone. Daily rescue medication usage was also reduced (-0.81 and -0.76 puffs per day for the two comparisons; both $p<0.001$).[19]

The LANTERN trial, comparing QVA149 against salmeterol + fluticasone in the broader COPD population, included patients with post-bronchodilator FEV_1 of 30–80% predicted and a history of one or more exacerbations. Dual bronchodilation was more effective at improving lung function than ICS/LABA, and reduced the time to first moderate or severe COPD exacerbations by 35% over 26 weeks of treatment (Figure 4; HR 0.65; p=0.028). Importantly, there were slightly fewer adverse events in patients treated with QVA149, but overall the regimens were similar. There was a reduction in incidence of

pneumonia in QVA149-treated patients compared to those on the ICS/LABA combination.[44] The FLAME study[45] is currently ongoing and is investigating QVA149 versus salmeterol/fluticasone in patients with a history of moderate-to-severe exacerbations.

Exacerbations are associated with increases in symptoms and comorbid events, with prior exacerbation being a major risk for future exacerbations. High-risk patients benefit from dual bronchodilation with QVA149, which is an effective therapy shown to both improve lung function and reduce exacerbations.

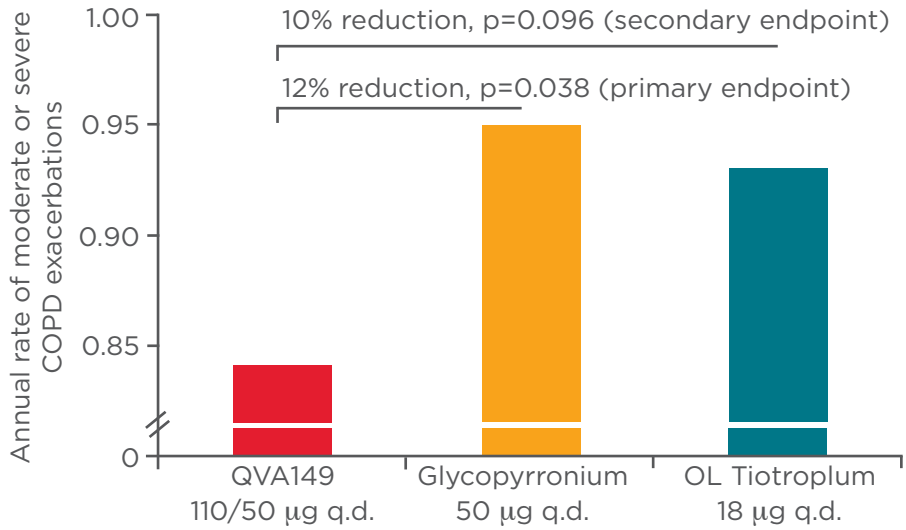
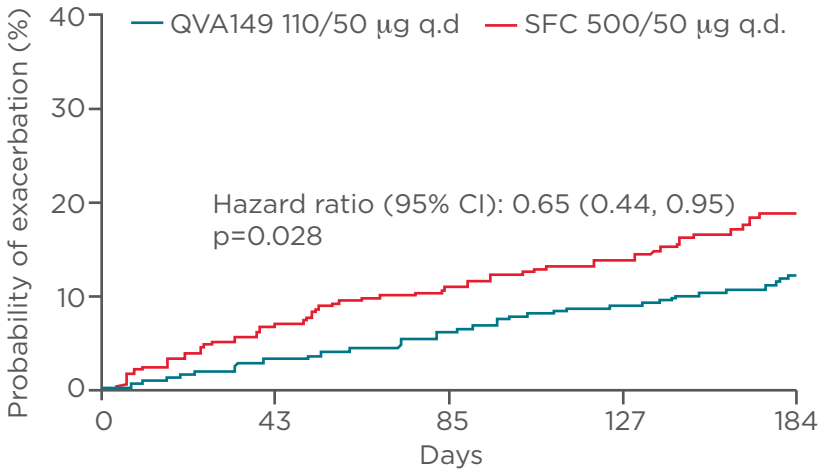


Figure 3: The SPARK study reached its primary endpoint of demonstrating superiority of QVA149 compared with glycopyrronium for the annualised rate of moderate-to-severe chronic obstructive pulmonary disease (COPD) exacerbations during the 64-week treatment period.

q.d.: quaque die (once daily); OL: open label.

Adapted from Lancet Respiratory Medicine, 1, Wedzicha et al., Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study, 199–209, 2014, with permission from Elsevier.



Patients with exacerbation (%)					
QVA149	0	12 (3.3)	20 (5.5)	31 (8.6)	43 (12.1)
SFC	0	24 (6.6)	38 (10.5)	48 (13.4)	67 (18.9)

Figure 4: QVA149 significantly reduced the time to first moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation compared to salmeterol + fluticasone in the LANTERN trial.

K-M: Kaplan–Meier; SFC: salmeterol/fluticasone propionate.

Adapted from Zhong N et al.[44]

Conclusions

Professor Bartolome Celli

COPD is a multi-dimensional, complex disease, but various disease characteristics help to assign patients to appropriate groups with therapeutic implications. Even though prognosis can be poor, COPD patients with poor status should be treated aggressively since not all patients decline equally; there are both rapid and non-rapid decliners, with average reduction in FEV_1 of 28 and 86 mL/year, respectively.[46]

Classification of patients into phenotypes may be of some use in order to identify which therapies to use. 'Rapid decliners' are those that are younger and who lose a large degree of lung function; this phenotype has not been studied as much as others. 'Hyperinflated' patients seem to have lung function as their major problem, but do not respond to anti-inflammatories since their disease is not one of severe inflammation. 'Exacerbators' may have to be approached differently to these other categories, and for 'co-morbid' patients COPD is not the driving force, meaning that individual therapy decisions will differ. Based on the COPD treatment algorithms there are now multiple possibilities for pharmacotherapy along with other treatment options such as rehabilitation, lung volume reduction surgery, oxygen supplementation, and azithromycin.

There is a continuing need to promote a healthy lifestyle and reduce smoking and air pollution, and improved diagnosis of COPD is required. Symptomatic patients on monotherapy or LABA/ICS should be considered for dual bronchodilation, and for patients with a high risk of exacerbations the data suggest this may also be a viable treatment option.

Summary of Q&A and Panel Discussion

Short-acting beta antagonists or short-acting muscarinic antagonists should only be used on an as-needed basis, not as a regular therapy.

The safety of LABA/LAMA combination is convincing in both older and younger patients; however, young people need to be active - increasing FEV_1 will improve QoL. Therefore younger patients may particularly benefit from combination therapy. Caution may be advised in prescribing LABAs/LAMAs in patients with significant underlying cardiovascular symptoms.

There is no difference between genders regarding the efficacy of dual bronchodilation.

Macrolides reduce exacerbations, likely through activity on infection but not on inflammation. There are, however, cardiac side-effects, and resistance is acquired quickly; it is suggested to use these drugs seasonally and not for long periods of time.

Theophylline has been used as a fourth-line agent on top of triple therapy, and is used very commonly outside of the USA. It may, however, increase mortality.

More needs to be learnt about when to use LABA/ICS; we now know that, before ICS, we can use LABA/LAMA, and ICS or other anti-inflammatories may be useful on top of dual therapies.

REFERENCES

1. Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369:448–57.
2. NYC Community Health Survey. Available at: http://www.nyc.gov/html/doh/html/data/survey.shtml.
3. Celli BR et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005–12.
4. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available at http://www.goldcopd.org.
5. Jones RC et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. Lancet Respir Med. 2014;2:267–76.
6. Tálamo C et al; PLATINO team. Diagnostic labeling of COPD in five Latin American cities. Chest. 2007;131:60–7.
7. Halbert RJ et al. Global burden of COPD: systematic review and meta-analysis. Eur Respir J. 2006;28:523–32.
8. Larsson ML et al. Passive smoking and respiratory symptoms in the FinEsS Study. Eur Respir J. 2003;21:672–6.
9. Tantucci C, Modina D. Lung function decline in COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:95–9.
10. Anthonisen NR et al. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002;166:675–9.
11. Hasegawa M et al. Relationship between improved airflow limitation and changes in airway calibre induced by inhaled anticholinergic agents in COPD. Thorax. 2009;64:332–8.
12. Cooper CB. Airflow obstruction and exercise. Respir Med. 2009;103:325–34.

13. Decramer M et al. Indacaterol therapy in patients with COPD not receiving other maintenance treatment. Respir Med. 2012;106:1706–14.

14. Kornmann O et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J. 2011;37:273–9.

15. D'Urzo A et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. Respir Res. 2011;12:156.

16. Kerwin E et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J. 2012;40:1106–14.

17. Buhl R et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. Eur Respir J. 2011;38:797–803.

18. Barnes PJ. Distribution of receptor targets in the lung. Proc Am Thorac Soc. 2004;1:345–51.

19. Wedzicha JA et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med. 2013;1:199–209.

20. Mahler DA et al. Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. Eur Respir J. 2014;43:1599–609.

21. Korn S et al. Once-daily QVA149 improves dyspnea, quality of life and reduces the rate of exacerbations compared to tiotropium plus formoterol in COPD patients: the QUANTIFY study. Poster A5982. American Thoracic Society (ATS) Conference, San Diego, California, USA, 16–21 May, 2014.

22. Calverley PM et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775–89.

23. Calverley P et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2003;361:449–56.

24. Mahler DA et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002;166:1084–91.

25. Szafranski W et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J. 2003;21:74–81.

26. Calverley PM et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J. 2003;22:912–9.

27. Hanania NA et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest. 2003;124: 834–43.

28. Doherty DE et al. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:57–71.

29. Nannini LJ et al. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;9:CD006829.

30. Price D et al. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. Prim Care Respir J. 2013;22:92–100.

31. Suissa S. Number needed to treat in COPD: exacerbations versus pneumonias. Thorax. 2013;68:540–3.

32. Vogelmeier CF et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med. 2013;1:51–60.

33. Small M et al. Quantification and treatment patterns of real-world patients classified by the GOLD 2011 strategy. Poster 185. British Thoracic Society Winter Meeting, London, UK, 5-7 December, 2012.

34. Frith P et al. Glycopyrronium once-daily significantly improves lung function and health status when added to fluticasone/salmeterol in patients with COPD: the GLISTEN study. Poster P2811. The European Respiratory Society Congress, Munich, Germany, 6–10 September, 2014.

35. Nadeem NJ et al. Withdrawal of inhaled corticosteroids in individuals with COPD--a systematic review and comment on trial methodology. Respir Res. 2011;12:107.

36. Magnussen H et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med. 2014;371:1285-94.

37. Lange P et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. Am J Respir Crit Care Med. 2012;186:975–81.

38. Hurst JR et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363:1128–38.

39. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet. 2007;370:786–96.

40. Seemungal TA et al. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161:1608–13.

41. Patel AR et al. Cardiovascular risk, myocardial injury, and exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;188: 1091–9

42. Maselli DJ et al. Risk factors and mortality associated with hospitalized chronic obstructive pulmonary disease (COPD) exacerbations during the 3-year follow-up in the evaluation of COPD longitudinally to identify predictive surrogate endpoints (Eclipse) cohort. Abstract A5374. American Thoracic Congress, Denver, Colorado, USA, 13–18 May, 2011.

43. Wedzicha JA et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177:19–26.

44. Zhong N et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol/fluticasone combination (SFC) in patients with COPD: the LANTERN study. Poster P2815. The European Respiratory Society Congress, Munich, Germany, 6–10 September, 2014.

45. Novartis Pharmaceuticals. QVA vs. Salmeterol/Fluticasone, 52-week Exacerbation Study. NCT01782326. http://clinicaltrials.gov/ct2/show/NCT01782326?term=COPD+novartis+52&rank=2.

46. Casanova C et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med. 2011;184:1015–21.