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REVIEW

Inhaled Corticosteroids for Chronic Obstructive Pulmonary Disease—The Shifting Treatment Paradigm

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Abstract

Chronic obstructive pulmonary disease (COPD) guidelines suggest using inhaled corticosteroids (ICS) in patients with severe airflow limitation or those at high risk of exacerbations. This recommendation is based on evidence demonstrating that ICS, especially when prescribed in fixed-dose combinations (FDC) with long-acting β2 agonists (LABA), improve quality of life (QoL), decrease exacerbations and hospitalisations, and have been associated with a trend towards a reduction in all-cause mortality. Audit shows that routine prescribing practice frequently uses inhaler therapies outside current guidelines recommendations; severe to very severe disease constitutes about 20% of all COPD patients, but up to 75% of COPD patients are prescribed an ICS, with significant numbers given ICS/LABA as first-line maintenance therapy. The role of ICS in the treatment paradigm for COPD is changing, driven by the growing evidence of increased risk of pneumonia, and the introduction of a new class of FDC; LABA and long-acting muscarinic antagonists (LAMA), which simplify dual bronchodilation and present a plausible alternative therapy. As the evidence base for dual therapy bronchodilation expands, it is likely that maximal bronchodilation will move up the treatment algorithm and ICS reserved for those with more severe disease who are not controlled on dual therapy. This change has already manifested in local COPD algorithms, such as those at Tayside, and represents a significant change in recommended prescribing practice. This review reassesses the role of ICS in the shifting treatment paradigm, in the context of alternative treatment options that provide maximal bronchodilation.

Abbreviations

COPD	chronic obstructive pulmonary disease
FDC	fixed-dose combinations
FEV_1	forced expiratory volume in one second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroids
INSPIRE	Investigating New Standards for Prophylaxis in Reduction of Exacerbations
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
MRC	Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NNH	number needed to harm
NNT	number needed to treat
QoL	quality of life
SABA	short-acting β2-agonist

Keywords: Chronic obstructive pulmonary disease, dual bronchodilation, inhaled corticosteroids, pneumonia

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SAMA	short-acting muscarinic antagonist
SAL	salmeterol
SFC	salmeterol/fluticasone propionate
SGRQ	St Georges Respiratory Questionnaire
TDI	transition dyspnoea index
TORCH	Towards a Revolution in COPD Health

Introduction

Important changes in our perspective and understanding of chronic obstructive pulmonary disease (COPD) have led to marked improvements in the treatment approach (1). Disease management has moved beyond spirometric parameters to include patient centred outcomes such as dyspnoea and exacerbation frequency, which are recognised as important elements in the assessment of treatment effectiveness, and there is acknowledgment of the importance of COPD phenotyping in optimising therapeutic options. In 2013, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) issued an updated document detailing the classification and treatment of COPD (1).

GOLD recommends classifying patients into one of four risk groups (A-D) using a combination of spirometry, symptoms and risk of future exacerbations. Treatment algorithms were suggested for each group, however bronchodilator therapy has remained the cornerstone of pharmacological management in all groups. Indeed, long-acting muscarinic antagonists (LAMA) are a first-line treatment option for any but those with mildest disease. GOLD suggests considering the use of inhaled corticosteroids (ICS) in patients with severe airflow limitation or for those who are at high risk of exacerbations. This is based on evidence demonstrating that ICS, especially when prescribed in fixed-dose combinations (FDC) with long-acting β_2 agonists (LABA), improve quality of life (QoL), decrease exacerbations, hospitalisations (2), and have been associated with a trend towards a reduction in all-cause mortality (3). Dual bronchodilation, through co-prescribing of LABA and LAMA, could be an alternative to ICS/LABA in certain COPD phenotypes. Also this approach could be used particularly in patients who remain symptomatic after LABA monotherapy, but who cannot tolerate or do not wish to take ICS. This concept, however, is not given the prominence it merits in the new GOLD, (1) or indeed other, guidance (1, 4).

The pivotal study which showed benefits of ICS/LABA, recruited participants with a forced expiratory volume in one second (FEV_1) of less than 60% predicted (3). There is no evidence supporting the therapeutic benefit of ICS/LABA in COPD patients with less severe airflow limitation, irrespective of exacerbation history (5). Despite this, ICS prescribing patterns demonstrate far wider application in COPD pharmacotherapy than recommended, with ICS/LABA a widely prescribed maintenance drug. Audit shows that routine prescribing practice frequently uses inhaled therapies outside current guideline recommendations; severe to very severe disease constitutes about 20% of all COPD patients, but up to 75% of COPD patients are prescribed an ICS, with significant numbers given ICS/LABA as first-line drug (6). This prescribing pattern may reflect the familiarity of prescribing ICS/LABA including historical prescribing where drug therapy is maintained because of disease stability, but it may also be a manifestation of physician concerns over the accuracy of diagnosis of COPD versus asthma resulting in continued ICS/LABA use.

The breadth of prescribing of ICS in COPD and lack of efficacy data in individuals with a $FEV_1 > 60\%$ highlights the need for the risk-benefit profile of ICS to be considered closely. ICS/LABA combinations are associated with a number of side effects beyond the topical effects of oral candidiasis and dysphonia, the most serious of which is an increased incidence of pneumonia (7). Randomised controlled trials and observational studies have persistently described the risk of pneumonia associated with ICS use, especially with fluticasone (3, 8). It has been suggested that there is an intra-class difference in ICS with respect to the risk of pneumonia; however, this is not a consistent observation (9). In addition, recent clinical trial data has suggested that the pneumonia extends to a new ICS currently in development (10, 11).

The evidence base for the efficacy and safety of dual bronchodilation has been limited until now (12). However the evidence for new LABA/LAMA FDC suggests a greater efficacy than LABA or LAMA monotherapy (13). This greater efficacy has been shown over a diverse range of clinically relevant outcomes, and identifies LABA/LAMA FDC as a potential new treatment option when trying to maximise symptom control and reduce exacerbations. This review reassesses the role of ICS in the shifting treatment paradigm, in the context of alternative treatment options that provide maximal bronchodilation.

Review

Inhaled corticosteroids in chronic obstructive pulmonary disease

Thirty years ago, ICS were established as effective treatments to reduce morbidity and mortality in asthma patients (14). This success prompted research into its possible therapeutic role in COPD, although initial evidence of efficacy was limited. The randomised controlled trials of ICS in COPD which followed in the 1990's had mixed results. There was no improvement in the rate of decline in lung function or exacerbation frequency when compared with placebo in studies of 6 months to 3 years duration (5, 15–19). It was not until ISOLDE (20); the first large, long-term, randomised, double-blind, placebo-controlled trial of ICS, that reduction in exacerbation rates and health care utilisation of ICS as therapy was described. From this point on, clinical trials

focused on assessing ICS/LABA combinations as well as ICS and LABA as monotherapy.

TRISTAN was one of the first, large (N = 1465), double-blind, randomised studies, which compared twice-daily salmeterol/fluticasone propionate 50/500 μg (SFC) to salmeterol 50 μg (SAL), fluticasone propionate 500 μg (FP) or placebo (21). Although the primary endpoint was pre-bronchodilator FEV_1, the number of exacerbations was an important secondary endpoint assessed at every clinic visit. All therapies improved lung function, symptoms, health status and reduced use of rescue medication and frequency of exacerbations compared to placebo; however combination therapy with SFC was more effective than salmeterol alone. The treatment effect was most pronounced in severe disease; those with a baseline FEV_1 < 50% showed a 30% reduction in exacerbation frequency with SFC compared to placebo, whereas there was only a 10% reduction in those patients whose FEV_1 > 50%.

The seminal TORCH trial (Towards a Revolution in COPD Health) followed several years later; this randomised 6112 patients to SFC (100/1000 μg/day), SAL (100 μg/day), FP (1000 μg/day) or placebo (3). All-cause mortality was the primary endpoint, with lung function, exacerbations and QoL reported over a period of 3 years. The SFC treatment group demonstrated, a 25% reduction in the annual rate of exacerbations (0.85 (95% CI, 0.80 to 0.90)) compared to placebo (1.13 (95% CI, 1.07 to 1.20)), with a number needed to treat (NNT) of four to prevent one exacerbation. At the same time, Kardos and colleagues compared SFC with SAL monotherapy in 994 patients with severe COPD for around 4 years (22). Combination therapy with SFC reduced the total number of exacerbations (334 vs. 464, $p < 0.0001$), the annual rate of moderate/severe exacerbations (0.92 vs. 1.4, corresponding to a 35% decrease, $p < 0.0001$) and the mean time to first exacerbation (128 vs. 93 days, $p < 0.0001$) (22).

A significant limitation of the studies described above is that they recruited patients based at least in part on an arbitrary FEV_1 cut off rather than the underlying phenotype ie emphysema or chronic bronchitis; it is well established that ICS will have beneficial effects in those with predominantly moderate degrees of airway obstruction and airway hyperresponsiveness or modest reversibility of FEV_1 (23). A lack of phenotyping is also present when it comes to exacerbations, many of the studies looking into the usefulness of ICS tend to simply group all exacerbations together, however this may limit a study's power to demonstrate ICS effectiveness. COPD exacerbations can be very different: infective (viral and/or bacterial), eosinophilic predominant or pauci-inflammatory (24). There is evidence that different treatments can be effectively adopted to reduce different COPD exacerbations, for instance, ICS added to long-acting bronchodilators can be utilised effectively to avoid eosinophilic exacerbations (25).

Summary evidence of the effect of ICS on COPD exacerbations is provided from recent Cochrane meta-analyses (2, 26). Analysis of 55 primary studies totalling 16,154 participants comparing any dose of any type of ICS with a placebo control in patients with COPD, showed long-term use of ICS significantly reduced the mean rate of exacerbations (generic inverse variance analysis: MD −0.26 exacerbations/patient/year, pooled means analysis: MD −0.19 exacerbations/patient/year) (20). In a pooled analysis of 5601 participants from 6 studies with predominantly poorly reversible, severe COPD, the use of ICS/LABA FDC significantly reduced exacerbation rates (rate-ratio 0.87, 95% CI 0.80 to 0.94) compared with ICS alone (26).

In terms of lung function and QoL, *post-hoc* analyses of TORCH reported an adjusted rate of decline in FEV_1 of 55 mL/year for placebo, 42 mL/year with FP or SAL, and for the combination of drugs a 39 mL per year decline, suggesting that treatment with ICS, LABA or the combination of two, can slow FEV_1 decline (27). The Cochrane analysis reported a pooled difference in rate of decline of post-bronchodilator FEV_1 of 6.88 mL/year (95% CI 1.80 to 11.96, 5 studies, 4823 participants) in favour of ICS (2). TORCH reported an improvement with SFC of 3.0 units of the St Georges Respiratory Questionnaire (SGRQ) compared to baseline after 3 years of treatment ($p < 0.001$ vs. placebo), with an improvement of 1.8 units in the fluticasone group ($p < 0.001$ vs. placebo); the placebo group showed a deterioration of 0.2 units in the SGRQ. The effect was largest in more severe COPD—an improvement in SGRQ of 5.9 units with combination therapy in stage 4, and 3.3 units with GOLD stage 3; in stage 2, the SGRQ improvement was less (2.3 units), but still significant (3). Despite these positive findings, the prescribing of ICS for COPD has remained a controversial subject (28, 29)

Safety profile of ICS treatment

The side effects of ICS treatment range from frequent unpleasant local side effects, such as oral candidiasis and dysphonia (2), to less common ones, such as adrenal suppression (30), cataracts (31, 32), and pneumonia (3, 8, 32–35). The side effect profile potentially extends to include osteoporotic fractures (2, 36) and increased diabetes risk (37, 38).

The studies of osteoporosis and fracture risk include combinations of randomised controlled trials and observational studies, each of which employed different definitions and therefore should be interpreted with caution. Several meta-analyses have reported conflicting results; Loke and colleagues found a modest but statistically significant increased likelihood of fractures in those treated with ICS (36); however, a Cochrane review reported that long-term studies which measured bone effects generally showed no major effect on fractures and bone mineral density over 3 years of follow-up (2).

Systemic corticosteroids are known to increase diabetes risk, but the impact of ICS is less well characterised. A large population based study of 388,584 patients with respiratory disease found treatment with ICS was

associated with a 34% (RR 1.34 (95% CI 1.29–1.39)) increased risk of new onset diabetes (defined by initiation of an oral hypoglycaemic agent), with the highest dose associated with the greatest risk (37). More recently, a retrospective study of administrative claims data from the Australian Government Department of Veterans' Affairs of more than 18,000 patients with diabetes, found there to be an increased risk of diabetes-related hospitalisations with the use of high-dose ICS (38). However, it is the increased risk of pneumonia which represents the greatest concern in regards to the use of ICS in COPD management.

ICS and pneumonia risk

Patients with COPD are at an increased risk of pneumonia due to the nature of the disease itself and risks may be further increased with ICS use. TORCH showed an increased rate of pneumonia among all patients receiving treatment containing ICS, with a two-fold higher rate of pneumonia compared with patients in the placebo arm (3), with a number-needed-to-harm (NNH) of 17 (33). A subsequent analysis of the TORCH data showed that the risk factors for ICS-associated pneumonia were increasing age, worsening spirometry, a history of COPD exacerbations in the year prior to the study, worse Medical Research Council (MRC) dyspnoea scores and a low body mass index; thus not dissimilar to the usual risk factors for pneumonia (39). The subsequent INSPIRE study (Investigating New Standards for Prophylaxis in Reduction of Exacerbations) comparing salmeterol plus fluticasone propionate 50/500 μg twice daily with tiotropium 18 μg once daily, reported double the rate of pneumonia with SFC (8%) than with tiotropium (4%) (34). The evidence of a dose-response for pneumonia risk comes from a nested case-control study of 175,906 patients, which found that the highest doses of ICS were associated with the highest rate-ratio for hospitalisation (rate-ratio of 2.25) (35). Summary evidence of the risk is provided by a Cochrane meta-analysis of 14 studies combining 11,794 patients, which reported moderate-level evidence of an increased pneumonia risk (by 50%) with ICS/LABA combinations versus LABA alone; however, mortality was identical between the treatment groups (23).

Randomised controlled studies of new agents currently in clinical development have also reported pneumonia. ILLUMINATE, a double-blind, double-dummy trial in 523 patients with GOLD stages II and III, without exacerbations in the previous year, compared once-daily LABA/LAMA FDC (QVA149 110/50 μg) or twice-daily SFC 50/500 μg for 26 weeks (40). Radiologically confirmed pneumonia was only reported in the SFC treatment group (four patients; 1·5%). A new ICS/LABA FDC, recently approved by the United States Food and Drug Administration (FDA) for the treatment of COPD—fluticasone furoate/vilanterol (FF/VI)—was assessed for exacerbation prevention in COPD patients with a history of exacerbations in two replicate, phase III randomised double-blind trials of 1622 patients (10). Three doses of fluticasone furoate were used (50 μg, 100 μg, and 200 μg) in combination with vilanterol 25 μg. Pneumonia and fractures were reported more frequently with FF/VI than with vilanterol alone. Eight deaths from pneumonia in the FF/VI groups compared with none in the vilanterol only group prompted discussion highlighting that the safety of ICS in COPD is a serious problem (11). The study was not powered to look at differences in pneumonia-specific mortality and overall mortality was not significantly different between the two groups. Interpreting the excess pneumonic episodes is complicated by the fact that ICS/LABA use in COPD decreases the rate of exacerbations and hospitalisations in clinical studies, and that no pneumonia deaths were identified secondary to SFC in TORCH (39). Reassuringly, a study looking at the impact of ICS use on outcome in COPD patients admitted with pneumonia did not show an association with worse mortality or the development of complications (41).

It has been suggested that ICS type may influence the risk, with some studies such as PATHOS suggesting that fluticasone carries a higher risk than others such as budesonide (8, 42). In this observational, retrospective cohort study, budesonide/formoterol or SFC were compared for pneumonia event rates, admission to hospital related to pneumonia, and mortality associated with pneumonia. SFC patients were significantly more likely to experience pneumonia and had a higher mortality related to pneumonia than patients treated with budesonide/formoterol. The authors offered plausible explanations for the observed difference, suggesting that the known immunosuppressant potency of fluticasone (10-fold higher than that of budesonide with regard to *ex vivo* inhibition of human alveolar macrophage innate immune response to bacterial triggers) could explain the findings. It must be noted that this was an observational study and that other studies of budesonide and mometasone in COPD have shown an increased rate of pneumonia associated with use of these agents (9, 43). The definitive answer as to whether this phenomenon is a class effect or one specific to fluticasone remains unclear.

ICS prescribing patterns

ICS's important but targeted role in COPD treatment is not reflected in prescribing patterns. In a large Italian study investigating whether pulmonologists follow GOLD recommendations when prescribing treatment for COPD, ICS alone and ICS/LABA combinations were over-prescribed in GOLD stages I and II, in patients without exacerbations in 40% and 64%, respectively. Overall, 62.1% of prescribing was not in keeping with GOLD recommendations (44). Similar findings were described in a French study, which found that more than half of all patients in GOLD class I and II were prescribed ICS (45).

Tayside Allergy and Respiratory Disease Information System (TARDIS) is a structured management

programme for patients with COPD (46). Patients are reviewed no less than once annually, and data on spirometry, exacerbations, and prescriptions, along with other variables is collected and recorded. A TARDIS study into the safety of β-blockers in COPD offered valuable insights into real life ICS prescribing patterns in Scotland. In this dataset of 5977 patients, the mean post-bronchodilator FEV_1 in patients receiving ICS as monotherapy was 65.3% and 63.1% in those patients receiving ICS/LABA FDC (47).

NICE (National Institute for Health and Clinical Excellence) COPD guideline recommend considering ICS/LABA FDC after short-acting β_2 agonists (SABA) or short-acting muscarinic antagonists (SAMA) in patients with FEV_1 < 50% predicted who have exacerbations or persistent breathlessness, and as a therapeutic option for those who have persistent exacerbations or breathlessness despite maintenance therapy with a LABA, irrespective of FEV_1 (4). According to GOLD, ICS/LABA is appropriate for patients with GOLD FEV_1 < 50% or in those at high risk of future exacerbations (1).

Clearly, ICS/LABA remains a valuable treatment option for selected patients with severe COPD or frequent exacerbations, however, phenotyping individuals to direct ICS therapy to those most likely to benefit is an important aim. As described above, COPD is a heterogeneous disease with clinically relevant phenotypes and these emerging phenotypes must be considered when planning therapeutic intervention. For example there is probably small benefit of prescribing high dose ICS to a COPD patient with predominant emphysema especially in the presence of relatively little airflow limitation while potentially exposing the individual to the risk of well recognized adverse side effects while at the same time ICS may potentially be used beneficially albeit without strict licensing criteria in non-smokers or ex-smokers with a relatively preserved FEV_1 but with symptoms secondary to recurrent eosinophilic COPD exacerbations.

Despite this, the current possibility of guideline concordant ICS prescription irrespective of FEV_1 moves ahead of the evidence, as the proven benefit of ICS is restricted to those with more severe airflow restriction. This is sustained in the opinion of the Scottish Medicines Consortium, which has restricted the license of ICS/LABA to individuals with a FEV_1 <50% (48). With emerging data on LABA and LAMA co-prescribing, both as free agents and FDC, the recommendation to consider dual bronchodilation only if ICS prescribing is not appropriate, will need to be altered in future guidelines. Important questions for guideline development groups to address will include establishing the role of dual bronchodilation in treatment algorithms in relation to ICS/LABA. This will involve only identifying which patients are most likely to benefit from dual bronchodilation and also taking into account factors such as risk and impact of side effects, symptoms and patient preference.

Subtle changes to the COPD guideline in Tayside were recently introduced to reflect current treatment options. ICS/LABA FDC are still recommended for persistent breathlessness or repeated exacerbations despite bronchodilator therapy (see step 4 in Table 1) with the proviso that ICS/LABA should only be prescribed if there are persistent symptoms and/or exacerbations despite *maximal* bronchodilator therapy (defined as co-prescribing of LABA and LAMA). In essence, LABA and LAMA co-prescribing has been 'pulled up' the treatment algorithm ahead of ICS/LABA, encouraging prescribing of ICS in patients with the most severe disease.

Table 1. COPD treatment algorithm employed by NHS Tayside.
The algorithm recommends that a combined inhaled steroid and long-acting bronchodilator should be prescribed only if the patient has persistent breathlessness or repeated exacerbations despite optimal bronchodilator therapy (defined in step 3 as LABA and LAMA co-prescribing, coloured blue) and should be discontinued if no benefit after 4 weeks

	Symptoms	Inhaled Medication[1]		
Step 1	Breathlessness and exercise limitation	SABA or SAMA as required		
Step 2	Persistent breathlessness and/or repeated exacerbations	SABA or SAMA as required	+	LABA
			Or	
		SABA as required	+	LAMA
Step 3[2]	Persistent breathlessness and/or repeated exacerbations despite treatment at step 2	SABA as required	+	LABA + LAMA
Step 4	Persistent breathlessness and/or repeated exacerbations despite treatment at step 3	SABA as required	+	ICS/LABA + LAMA

ICS, inhaled corticosteroids; LABA, long-acting β2-agonist bronchodilator; LAMA, long-acting anti-cholinergic; SABA, short-acting β2-agonist bronchodilator; SAMA, short acting anti-cholinergic

[1]Consider administration via an MDI and spacer at each step when:
The inspiratory flow rate is < 30 L/min.
Poor technique with dry powder device.
Recurrent candidiasis of the mouth or throat.
Medication is carer administered.
Unlikely to generate sufficient inspiratory flow when exacerbating.

[2]Theophylline use.
Oral slow release theophylline (Uniphyllin® m/r tablets) may be useful after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy. Monitoring plasma levels of theophylline is not routinely necessary in stable patients but may be warranted in certain circumstances, eg, a change in clinical status, where toxicity is suspected or during concomitant use of interacting drugs.

Combining LABA and LAMA in COPD

The rationale for co-prescribing of LABA and LAMA is clear; combining long-acting bronchodilators with distinct, complementary and possibly synergistic mechanisms of action, has the potential to maximise bronchodilator response. Muscarinic receptor antagonists inhibit bronchoconstriction by inhibiting the binding of acetylcholine to muscarinic receptors on airway smooth muscle. β_2-agonists directly activate β_2-adrenoreceptors, causing airway smooth muscle relaxation. Therefore, by simultaneously addressing both mechanisms of bronchodilation, one can potentially modulate against the inter-patient and intra-patient variability in response to individual agents (49). This should lead to a bronchodilator response which would not otherwise be seen if one or other agent were prescribed alone. Clinical studies have shown this potentially synergistic effect of co-prescribing, in which the combined treatment effect of LABA and LAMA is greater, or longer-lasting than expected from single agent bronchodilation. This may relate to M_3-receptor blockade by LAMA amplifying and prolonging LABA-induced β_2-adrenoreceptors activation (50), and provides mechanistic support for the potential of LABA and LAMA inhaled combinations.

At least 12 randomised clinical trials have set out to investigate clinical outcomes after LABA and LAMA co-prescribing (formoterol, arformoterol, or indacaterol co-prescribed with tiotropium)(51). The largest of these, INTRUST-1 and INTRUST-2 trials, randomised 1134 and 1142 patients with moderate to severe COPD respectively, already receiving open-label tiotropium 18 µg, to indacaterol 150 µg once-daily or placebo for 12 weeks (52). Concurrent use of indacaterol plus tiotropium provided superior bronchodilation compared with tiotropium alone, increasing the FEV_1 AUC by 130 and 120 mL, trough by 80 and 70 mL ($p < 0.001$) and trough IC by 130 and 100 mL ($p < 0.01$). Importantly, the adverse event (AE) profile was similar between treatments except cough, which was more common in the LABA plus LAMA patients. Meta-analysis of eight randomised trials of tiotropium plus formoterol, compared with tiotropium alone, including 1868 patients with stable COPD, found that treatment with tiotropium plus formoterol improved lung function (weighted mean difference in FEV_1 of 105 mL) and symptom scores (weighted mean difference in transitional dyspnoea index (TDI) of 1.5). However, there was no significant reduction in exacerbations seen when compared to treatment with tiotropium alone (53). There was a trend towards a decrease in adverse events, although this was not statistically significant.

LABA and LAMA fixed-dose combinations

The development of a LABA/LAMA FDC is a simple way of ensuring that medication burden is reduced (single inhaler vs. multiple inhalers) thus minimising the risk of non-compliance. The challenge in the development of FDC inhalers is ensuring the balance between drug efficacy and side effect profile. This includes determining the minimally effective doses of LABA's and LAMA's in combination preparations, accepting that they may not be the same as in monotherapy preparations due to combination pharmacodynamics.

A number of LABA/LAMA FDC are currently in clinical development (Table 2). One combination, known as QVA149 (Ultibro®, Novartis), a FDC of indacaterol (110 µg) and glycopyrronium (50 µg), is the first once-daily dual agent bronchodilators to be approved for clinical use in Europe. The FDC of a LAMA, umeclidinium (UMEC), and a LABA, vilanterol (VI) (62.5/25 µg), known as UMEC/VI (Anoro, GlaxoSmithKline), was approved by the FDA in December 2013, by the EMA in May, 2014 and in Japan in July, 2014. In a recent study, the use of once-daily UMEC/VI FDC over 24 weeks resulted in significant improvements of trough FEV_1 when compared to placebo as well as monotherapy of the individual components (54).

In Phase II studies, QVA149 showed a fast onset of action with a statistically significant ($p < 0.0001$) increase in FEV_1 over placebo, indacaterol (300 µg and 600 µg) 5 minutes post-dose on day 1 and a significant ($p < 0.05$) increase in FEV_1 over placebo, indacaterol (300 µg and 600 µg) at all time-points on day 1 (55). In a cardiovascular safety-orientated trial, QVA149 was well tolerated with an acceptable AE profile (56).

Table 2. LABA/LAMA fixed-dose combinations in late-stage clinical development

Combination	Development phase	Company	Pivotal trials
Indacaterol/glycopyrronium (QVA149)	110/50 µg approved (EU, Japan)	Novartis	IGNITE program 11 trials, 11,000 patients
Umeclidinium/vilanterol	62.5/25 µg approved (US, EU, Japan)	GSK, Theravance	Phase III program 7 trials, 6000 patients
Olodaterol/ tiotropium	5 /5 µg filed in EU, US	Boehringer Ingelheim	TOviTO program Several trials, 5000 patients
Aclidinium/ formoterol	400/12 µg (bid) Filed in EU	Almirall, Forest	ACLIFORM (NCT01462942), AUGMENT (NCT01437397) LAC-MD-32; LAC-MD-36
Formoterol/ glycopyrronium	Phase III	AstraZeneca	PINNACLE 1 (NCT01854645) PINNACLE 2 (NCT01854658) Safety extension (NCT01970878)

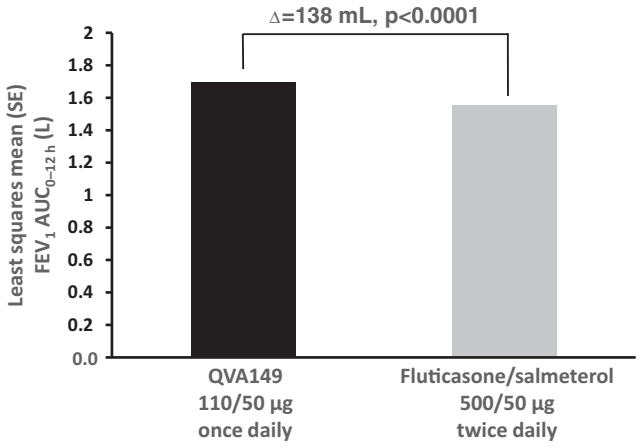

Figure 1. Comparison of FEV_1 for QVA149 versus fluticasone/salmeterol. The ILLUMINATE double-blind, randomised trial of 523 patients. The primary study endpoint was FEV_1 $AUC_{0–12\,h}$ at 26 weeks for QVA149 vs. salmeterol/fluticasone (40). At Week 26, FEV_1 $AUC_{0–12\,h}$ was significantly higher with QVA149 compared with fluticasone/salmeterol combination, with a significant and clinically meaningful treatment difference of 138 mL (95% CI 100–176; $p < 0.0001$).

QVA149 is being investigated in a large ongoing, Phase III programme called IGNITE comprising 11 studies of more than 10,000 patients. One trial (ILLUMINATE) compared QVA149 with SFC in 523 patients with no history of exacerbations within the preceding year in a double-blind, double-dummy, parallel-group design (40). QVA149 provided significantly better, clinically relevant improvements in lung function with a rapid onset of action; at 26 weeks, FEV_1 $AUC_{0–12h}$ was significantly higher with QVA149, with a treatment difference of 0·138 L ($p < 0·0001$ versus SFC) (see Figure 1). Significant improvements in TDI scores, with a treatment difference of 0.76 ($p = 0.003$ versus SFC), and reduced use of rescue medication was also seen with QVA149. The study design allowed insights into the impact of ICS withdrawal—at Week 26 patients who had been on ICS therapy at enrollment showed similarly higher values for FEV_1 with QVA149 compared with SFC to those who had not been on ICS treatment. This study supports the approach of using one or more bronchodilators for symptomatic COPD at low risk of exacerbation without ICS.

Conclusion

The role of ICS in the treatment paradigm for COPD is changing. This is driven by the growing evidence of increased risk of pneumonia, and a new class of LABA/LAMA FDC which simplifies dual bronchodilation, presenting a plausible alternative for some patients. As the evidence base for dual bronchodilation expands, it is likely that maximal bronchodilation will move up the treatment algorithm, with ICS reserved for those with more severe disease who are not controlled on dual therapy or where the clinical phenotype is known to receive therapeutic benefit. This change has already manifested in some COPD algorithms, such as those at Tayside, representing a significant change in recommended prescribing practice. Co-prescribing of LABA and LAMA is utilised much less frequently than LAMA monotherapy, ICS/LABA combinations, and the triple combination of LAMA plus ICS/LABA in recent reviews of prescribing practice (12).

The key issue is the balance of risk-benefit of ICS in individual patients; the risk of pneumonia versus the benefit of reduced exacerbations. With the availability of new FDC, dual bronchodilation can be prescribed without increasing the dose of the LABA or LAMA component, and delivered in a simple, once-daily dosing regimen as a single inhaler. The once-daily dosing may be quite important for COPD patients, with evidence suggesting that compliance and adherence to treatment plans is historically poor, with COPD patients particularly vulnerable to treatment adherence lapses (57). However, further data of the equivalence of LABA/LAMA with ICS/LABA in respect to exacerbation frequency is required.

For those patients already receiving ICS, the key concern is the risk of precipitating an exacerbation by ICS cessation, therefore careful review and individualised patient management is required. A patient's response to treatment, their preference, the likely side effects, the risk of exacerbation and financial cost implications require consideration. However for those patients with $FEV_1 > 50\%$ without frequent exacerbations, it is likely that the risk-benefit is in favour of considering stopping ICS treatment. ICS withdrawal may be associated with worsening of COPD control so must be done carefully (58). For those patients with the most advanced disease, triple therapy will remain the preferred treatment. The optimal posology of triple drug treatment requires further consideration, with the likely scenario of LABA/LAMA FDC co-prescribed with an ICS in a single inhaler emerging as the preferred option.

Declaration of Interests Statement

Aidan McManus, PhD CMPP and Ana Martins-Kaczor, PhD assisted Drs. Wilkie and Schembri to write a first draft of the manuscript based on a transcript and PowerPoint presentation given by Dr. Schembri, and provided subsequent editorial support as directed by Dr. Schembri. This editorial assistance was funded by Novartis UK, who reviewed the manuscript for medical accuracy but not content. These individuals did not meet the ICMJE criteria for authorship (www.icmje.org/).

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Authors' Contributions

Dr. Stuart Schembri conceived the review and its content, including all interpretation of the studies described, based on a presentation given at a COPD meeting in Scotland in June, 2013. Dr. Morven Wilkie and Dr. Simon Finch reviewed and commented on the first draft and approved the final version.

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