COPD pharmacological treatment: efficacy and tolerability profiles in the elderly patient. Focus on aclidinium bromide

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is expected to become the third cause of death due to continued exposure to risk factors for COPD such as cigarette smoke, to the reduction in all cause mortality and to an ageing world population. The ageing of airways and of lungs lead to structural alterations that are similar to those observed in COPD, for instance the progressive reduction in the thorax wall compliance, the reduction in respiratory muscle strength and the anatomical changes of pulmonary parenchyma and peripheral airways that in the end lead to lung hyperinflation. All these different aspects cause relevant symptoms that have a critical impact on patient’s quality of life related to the health status. In this context the pharmacological treatment choice has to take into account the effectiveness in symptoms control during the most critical part of the day, such as in the morning, the capability to reduce lung hyperinflation, breaking down a vicious circle that starting form dyspnoea lead to muscle deconditioning and to an augment in exacerbation rates, with a worse prognosis. Among the new bronchodilators, aclidinium owing to its pharmacological properties and the well documented efficacy and safety profile.

Key words: COPD, Ageing, Symptoms, Quality of Life, Aclidinium, Effectiveness, Safety

DAILY VARIABILITY OF COPD SYMPTOMS

Along with ageing lung residual volume increases while reserve volumes (inspiratory and expiratory) decrease.
owing to a progressive lost of elastic recoil of lung tissue. Typically, COPD is characterized by an increase in residual volume and a reduction in inspiratory capacity. Airflow limitation is the common denominator of this respiratory disease. The narrowing of periferal airways reduces air flow during expiration (FEV1). Progressive obstruction of distal airways entraps the air during expiration causing hyperinflation, which in turn decreases inspiratory capacity and increases residual functional capacity especially during physical exercise depicting a picture of dynamic hyperinflation.

In airways, prenchyma and lung blood vessels it is possible to observe typical anatomo-pathological alterations in the lung that include chronic inflammmation with an increased presence of inflammatory cells (polimorphonuclear neutrophils, macrophages, CD8+ and CD4+ T cells, B cells and follicle reach lumphoid aggregates) and structural alterations caused by a process characterized by repeated damages and repairing attempts.

Anatomo-pathological alterations are related to a symptoms burden characterized by circadian variability. A cross-sectional, observational pan-European study that involved 2441 COPD patients in 17 Countries recruited through telephone interviews and aimed to evaluate symptoms variability in every day life during a 7 days observation period, has shown that the majority of patients (92.5%) has at least one COPD-related symptom most frequently dyspnoea reported by 72.5% of patients, followed by phlegm, cough, wheezing or chest tightness (Fig. 1).

In the study by Kessler and colleagues, 62.7% of symptomatic patients overall reported a daily or weekly perceived symptoms variability, pointing at dyspnoea as the most variable symptom during the week or during the same day. Patients reported a higher symptoms perception in the first morning hours. As a whole, the percentage of patients who reported troublesome symptoms at awakening in the morning and during the day was 45.4% as regards breathlessness, 60.1% as concerns cough, 70.9% for fatigue, 45.4% for chest tightness and 43.4% for wheezing. Night time as well has been indicated as a troublesome period for symptoms that have compromised sleep quality in 26.5% of patients.

These observations confirm the results of the study by Partridge and coworkers conducted through a web survey on 803 european and american COPD patients. This study has shown that the morning is the worst period of the day for symptomatology onset, especially for patients with severe COPD. Breathlessness has been the most frequent symptom reported, strictly associated with morning activities limitation.

Figure 1. Symptoms variability in COPD patients: observational pan-European study (from Kessler et al., 2011, mod.).

Morning and night time symptoms importance comes to light also from the results of a trial conducted in 85 centers in various European countries, that has evaluated prevalence and severity of night time, morning and day time symptoms in patients receiving treatment for stable COPD. The study has included 727 patients (65.8% males, mean age 67.2 years, FEV1 52.8% of predicted). In each analyzed moment of the day (night, morning, day) more than 60% of patients reported one or more symptoms in the previous week, with a higher frequency during the morning (81.4%) and during the day (82.7%). In the week before the inclusion in the trial, 90.5% of patients suffered some symptoms at least in one part of the day; in more than half of the patients (56.7%) symptoms were present early in the morning, during the day and the night time periods wile only 10.6% of the patients was symptomatic solely in one period during 24 hours.

A significant relationship (p < 0.001) has been shown between night, morning and day time symptoms and dyspnoea severity, sleep disturbs, anxiety or depression severity and health status.

Dyspnoea greatly contributes to the disease burden and to the poor quality of life reported by patients. Breathing difficulty is a consequence of a reduced respiratory capacity linked to the reduction in the lung elastic recoil, to the narrowing of airways lumen and to the increase in airflow resistance, to the expiratory flow-limitation and to the consequent static and dynamic hyperinflation. This implies a reduction in physical exercise capability and muscular deconditioning in a vicious circle.

The dyspnoea severity is, anyway, scarcely related to FEV1 modifications and this is clearly shown also by
the efficacy of bronchodilator drugs, that are able to reduce pulmonary hyperinflation, even in presence of moderately altered FEV₁ values. FEV₁ poorly correlates to quality of life, as shown by basal values of St. George Respiratory Questionnaire (SGRQ) and FV1 in 800 patients included in ISOLDE trial 20.

Quality of life is on the contrary strongly influenced by symptoms variability. A study in which a specific questionnaire aimed to evaluate the impact of symptoms on morning activities has been applied, showed that morning symptoms have the strongest impact on common living activities 21, a result suggesting that treatment capable of influencing symptoms perception can potentially ameliorate HRQL 22.

**EXACERBATIONS AND QUALITY OF LIFE**

COPD exacerbations prevention is one of the main goals of the treatment of this respiratory disease 23. Exacerbations have a heavy impact on QoL of patients as well on natural history of the disease, as clearly demonstrated in a trial by Seemungal and coworkers 24. In this study, 70 COPD patients (52 males, mean age 67.5 ± 8.3 years, FEV₁ 1.06 ± 0.45 L, FVC 2.48 ± 0.82 L, FEV₁/FVC 44 ± 15%, FEV₁ reversibility 6.7 +/- 9.1%, PaO₂ 8.8 +/- 1.1 kPa) were followed for one year during which peak expiratory flow (PEF) was measured on a daily base. Sixtyone patients (87%) experienced 190 exacerbation overall (3 exacerbation/patient as a mean) during observation period. Each exacerbation was associated with an average fall in PEF of 6.6 l/min (p = 0.0003). Dividing the patients on the basis of exacerbations number into frequent (3-8 events) or infrequent (0-2 events) exacerbators, the Authors showed that the SGRQ total and component scores were significantly worse in the group that had frequent exacerbations: SGRQ total score (mean difference = 14.8, p < 0.001), symptoms (23.1, p < 0.001), activities (12.2, p = 0.003), impacts (13.9, p = 0.002). Factors considered predictive of frequent exacerbations were daily cough (p = 0.018), wheeze (p = 0.011), and cough and sputum (p = 0.009) and frequent exacerbations in the previous year (p = 0.001). These findings suggest that patient QoL is related to COPD exacerbation frequency. Exacerbation onset, on the other hand, is a crucial moment per se because it modifies the disease course and it is associated with a worse prognosis. Soler-Cataluna and colleagues have shown that mortality rate increases with the increase in exacerbations frequency, especially when a hospitalization is needed 25. The Spanish prospective study was performed in a cohort of 304 male patients with stable COPD, mean age 71 ± 9 years. The frequent exacerbators (3 or more exacerbations/year) requiring hospitalization were those with the higher mortality rate (p < 0.001) with a risk of death 4.30 times greater (95% CI 2.62 to 7.02) than that for patients not needing hospital management. The patients with 2 or less exacerbations per year had also a 2.20 times (95% CI 1.45 to 3.33) higher risk of death than those not hospitalized. Even patients with only one hospital admission had worse survival than those with no acute exacerbations of COPD (HR 2.94, 95% CI 1.82 to 4.72) (Fig. 2). The lowest survival rate was observed in patients requiring hospital readmission (HR 4.31, 95% CI 2.70 to 6.88). The observed increase in mortality following severe exacerbations requiring hospitalization is probably related to baseline severity of the disease which is linked to risk factors such as advanced patient age, hypoxaemia, hypercapnia, BMI, comorbidity, cor pulmonale, or sustained oral corticosteroid treatment. Exacerbations are also related to lung function reduction: in patients affected by severe COPD it has been demonstrated that frequent exacerbators have a faster decline in respiratory function parameters than those who have less exacerbations during a year 26. A study by Donalson and colleagues conducted on 109 COPD patients, mean age 68.1 years (63-74 years), has shown that those with frequent exacerbations (> 1.5/year) had a significant faster decline of FEV₁ and PEF of -40.1 ml/year and -2.9 l/min/year respectively compared to infrequent exacerbators (< 1.5 exacerbations/year), who experienced reduction in FEV₁ of -32 ml/year (n = 162) and in PEF of -0.7 l/min/year (n = 63) (p < 0.05 and p < 0.001 respectively).

Exacerbation that sprinkle natural course of COPD are associated with an increased risk of myocardial infarction (MI) and stroke. Donaldson and coworkers have analyzed the data of 25,857 patients included in The
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Health Improvement Network database, finding that MI risk after 1 to 5 days from an exacerbation event increased 2.27 times (95% CI, 1.1-4.7, p = 0.03) and stroke risk after 1 to 49 days from an exacerbation increased 1.26 times (95% CI, 1.0-1.6, p = 0.05) \(^{27}\). This study proves that after exacerbation patients are at particular risk of cerebral-and cardiovascular events and this aspect can have implications on COPD therapy.

Another study by McAllister and colleagues on 242 COPD patients (mean age 69 ± 9 years) hospitalized for an exacerbation showed that 1 out of 12 patient had symptoms or signs suggestive of MI \(^{28}\). Exacerbations repercussion on cardiovascular system springs also out from a study showing that patients with frequent moderate exacerbations have a more pronounced arterial stiffness than infrequent exacerbators; during exacerbation arterial stiffness has been shown to increase particularly in presence of airways infections \(^{29}\). Arterial stiffness increase is also related to inflammation degree and regresses slowly in several weeks.

A more pronounced arterial stiffness increases myocardial workload requested to overcome high systolic aortic pressure and decreases coronary blood flow. The mechanism that links together airways infections, airways and systemic inflammation, arterial stiffness increase and myocardial damage has not yet been clearly defined but it may include sympathetic system hyperactivity, nitric oxide availability and endothelial dysfunction.

Airways infections play anyway a crucial role in exacerbations onset. As Papi and colleagues have demonstrated in a clinical trial conducted on 64 patients hospitalized for a COPD exacerbation, respiratory infections are associated with COPD exacerbations majority and seriousness, especially in case of viral and bacterial co-infection, present in 25% of patients, whereas an isolated viral infection has been demonstrated in 24% of patients and a bacterial infection in 30% \(^{30}\). In an experimental model, rhinovirus infection in COPD patients has been shown to induce symptoms and lung function modifications usually observed in case of exacerbation, pointing out an evidence of a causal relationship \(^{31}\).

COPD course implies a rapid health status decline after the second severe exacerbation and a high mortality in the weeks following each severe exacerbation. Mortality related to the second severe exacerbation has been shown to be 1.9 times higher than that related to the first exacerbation and mortality related to the tenth exacerbation has been demonstrated to be 5 times higher than the first \(^{32}\). Two strategic goals of COPD management should therefore include the delay in severe exacerbation onset and the improvement in exacerbations treatment in order to reduce early mortality.

**THERAPEUTIC MANAGEMENT OF ELDERLY PATIENT**

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations in order to properly define the influence of COPD in each patient it is necessary to implement a combined evaluation approach that put together symptoms burden with spirometric results and/or exacerbation risk \(^{23}\). This approach, along with the evaluation of potential comorbidities, reflects COPD complexity in a better way than a monodimensional analysis such as the airflow limitation previously used to stage the disease and lays the foundations for a tailored treatment choice.

COPD pharmacologic therapy has the goals to reduce symptoms burden, exacerbation frequency and severity, to ameliorate patient’s global health status and tolerance to physical strain \(^{23}\). Bronchodilators are the cornerstone in the pharmacological treatment of COPD \(^{33}\). These drugs allow pulmonary desufflation, a lung volumes reduction both in static and dynamic conditions, a dyspnoea reduction both at rest and during exercise and an increase in physical exercise tolerance.

A crucial aspect of COPD treatment is exacerbation prevention and this regards it must be said that available pharmacologic options have shown to be effective. In TORCH study, for instance, the combination regimen of salmeterol at a dose of 50 µg plus fluticasone propionate at a dose of 500 µg twice daily administered with a single inhaler in a 3 years period significantly reduced exacerbations frequency compared to placebo and compared to single therapies (from 1.13 to 0.85 exacerbations/patient/year combination regimen vs placebo, p < 0.001; from 0.97 to 0.85 exacerbations/patient/year combination regimen vs salmeterol, p = 0.002; and from 0.93 to 0.85 exacerbations/patient/year combination regimen vs fluticasone, p = 0.0024), though combination regimen did not significantly reduced all cause mortality compared to placebo (95% CI 0.681-1.002, p = 0.052) \(^{34}\). The combination of budesonide/formoterol 160 µg/4.5 µg bid has also demonstrated to reduce the exacerbations number compared to monotherapies and to placebo (all p < 0.005) and to stabilize respiratory function \(^{35}\).

In another trial, a combination of an inhaled corticosteroid (ICS) and a long acting beta2-adrenergic agonist (LABA) reduced by 24% the mean exacerbation number per patient per year compared to placebo and by 23% compared to formoterol, while increased FEV, by 15% versus placebo and by 9% versus budesonide \(^{36}\). In both studies the combination regimen has significantly improved the overall symptomatology compared to single therapies, while SGRQ score was reduced more
than 4 points – considered as a cutoff value for a perceived beneficial effect of therapy by patients – only in the study by Calverley (-7.5 points) but not in the one by Szafranski (-3.9 points).

A relevant aspect concerns the onset of adverse events (AE). In TORCH study 41% of patients developed a severe EA, in most of the cases related to an exacerbation. These considerations must be taken into account especially for the treatment of elderly patients, who frequently are included in groups B and D – that is more symptomatic patients – according to combined evaluation criteria of GOLD recommendations. In these patients it is of particular usefulness the administration of bronchodilator agents that allow a good symptoms control along the whole day and especially during the morning, with a good safety profile.

In treatment choice it is important to consider that the faster is the pharmacological effect onset of a therapeutic agent the greater is the impact on morning symptoms, with positive consequences on HRQL 6. The rapid action onset bronchodilators nowadays available, including LABAs such as formoterol and indacaterol, and LAMAs, such as glycopyrronium and aclidinium, could play a key role in the improvement of morning symptoms control symptoms and HRQL in COPD patients 6.

Aclidinium, in particular, is a long acting muscarinic antagonist with a new chemistry structure that contains a (3R)-quaternized quinuclidine ester. It is important to remember that the parasympathetic activity in respiratory airways induces smooth muscle cells contraction and mucus secretion. These effects are mediated by the action of acetylcholine (Ach) on M3-type receptors. By contrast, ACH action on M2-type receptors inhibits the release of more ACH from nerve endings. This in turn causes a reduction in free Ach available to a link to M2-type receptors, inhibiting this way smooth muscle cells contraction 37.

Aclidinium exerts its effects through a selective antagonism on M2-type receptors. This molecule has a long residency half-life at the M3 receptor; the slow dissociation time prolongs the action of the drug. On the contrary, aclidinium has a short residency half-life at the M2 receptor, thus showing a kinetic M2/M3 selectivity 38.

Aclidinium is rapidly hydrolyzed in human plasma with an half-life of 2.4 minutes, where more then 70% of tiotropium or ipratropium are not modified in human plasma after a 60 minutes incubation 39. Aclidinium has shown good efficacy and safety profiles in clinical trials. In the double-blind ATTAIN trial, 828 patients with moderate or severe COPD were randomized (1:1:1 ratio) to receive aclidinium 200 µg or 400 µg BID or placebo for 24 weeks 40. The primary efficacy endpoint was the change from baseline in morning pre-dose (trough) FEV1 at week 24.

Aclidinium 200 µg and 400 µg BID significantly improved trough FEV1, compared with placebo (p < 0.001 for both). The magnitudes of the improvements over placebo were 99 mL and 128 mL for the 200 µg and 400 µg doses, respectively (Fig. 3).

Pre-dose morning FEV1 improvement with both aclidinium dosages was significantly greater compared to placebo in each time interval from Week 1 to Week 24 (p ≤ 0.0001 for all).

A modification from baseline in mean SGRQ total score during study period was a secondary endpoint. A reduction ≥ 4 units represents a clinical significant improvement. At week 24, the improvement over placebo in baseline-adjusted mean SGRQ total score was -3.8 units for aclidinium 200 mg (p < 0.001) and -4.6 units for aclidinium 400 mg (p < 0.0001). The most frequently reported AE was exacerbation of COPD (n = 16; 1.8%) and the incidence was higher in the placebo group than in the aclidinium 200 µg and 400 µg groups (3.7%, 1.4% and 0.7%, respectively). Potential anticholinergic AEs occurred at a similar low incidence (< 2.5% of patients) in each treatment group. Aclidinium has shown a favourable cardiovascular safety profile.

In the phase IIa randomized, double blind, crossover LAS-23 trial, 30 patients with moderate to severe COPD received aclidinium 400 µg bid, tiotropium 18 µg once daily, and placebo for 15 days, with a 9 to 15 day washout between three treatment sequences 41. On day 1 the variation from baseline in normalized FEV1 AUC0-12/12 was significantly greater with aclidinium 400 µg compared to placebo (230 mL vs 16 mL; p < 0.0001). Aclidinium 400 µg induced a significantly greater bronchodilation than placebo in each time sequence considered on day 1 (p < 0.001). On day 1 aclidinium 400 µg induced also a significantly greater bronchodilation compared to tiotropium during night time (13-22 hours after morning dose administration) (p < 0.05). Difference in FEV1 AUC0-12/12 of aclidinium and tiotropium was 101 ml (p < 0.01) on day 1 (Fig. 4). On day 15 as well the variation from baseline in normalized FEV1 AUC0-12/12 was significantly greater with aclidinium 400 µg compared to placebo (236 mL vs 15 mL; p < 0.0001).

Aclidinium 400 µg induced also a significantly greater bronchodilation compared to tiotropium during night time (13-22 hours after morning dose administration) on day 15 (p < 0.05). Difference in FEV1 AUC0-12/12 of aclidinium b and tiotropium was 78 ml (p < 0.05) on day 15.

It has been shown in different conditions that a poor sleep quality deteriorates health status. A study conducted on 2.848 COPD patients managed in a a
primary care setting revealed that 67% of patients had symptoms during the night. The percentage of patients with nocturnal symptoms increased with the worsening of COPD. Patients who experienced symptoms during the night and the morning had a more severe daytime dyspnea and an increased exacerbations rate than patients with only daytime symptoms. Furthermore, patients with both nocturnal and diurnal symptoms needed more maintenance therapies compared to those with only with daytime symptoms. ACCORD COPD1 study has demonstrated that aclidinium improves nocturnal symptomatology. In this double-blind study, 561 patients were randomized (1:1:1) to receive for 12 weeks aclidinium 200 μg or 400 μg twice daily (BID) or placebo. Primary efficacy endpoint was the variation from baseline in pre-dose morning FEV1 (trough) on week 12. Aclidinium at both dosages significantly improved pre-dose morning FEV1 compared to placebo (p < 0.001 for both dosages). The improvement amount compared to placebo was 86 ml with 200 μg and 124 ml with 400 μg. Nocturnal and early morning symptoms were registered each morning with COPD nocturnal symptoms questionnaire, filled by patients themselves through an electronic log. On week 12, treatment with aclidinium 200 μg and 400 μg significantly reduced mean daily nocturnal COPD symptoms frequency (night dyspnea, cough, sputum production and wheezing) compared to placebo (p < 0.05, 200 μg and p < 0.01, 400 μg). Morning symptoms improved significantly as well (Fig. 5, 6).

Secondary endpoint was the percentage of patient with a clinical significant improvement in SGRQ total score (clinical relevancy for a modification of ≥ 4 units from baseline) on week 4, 8 and 12. Both aclidinium dosages produced a significant improvement from baseline in SGRQ total score on each time point (p < 0.05 for all). The treatment was well tolerated. The incidence of anticholinergic AEs was low and similar across groups (dry mouth: 0.5%-1.6%; constipation: 0%-1.1%). Exacerbation onset was observed in 12.4% in placebo group, in 9.2% in aclidinium 200 μg group and in 7.4% in aclidinium 400 μg group.

An effective and persistent bronchodilation is a key point in order to improve dyspnoea and physical performance in COPD patients. The combination of LABA and LAMA at low doses can optimize the bronchodilation both in patients with a less severe disease by reducing the risk of adverse events related to single agents at full dose, and in severe COPD patients not controlled by monotherapy.

Fixed dose combinations (FDC) of bronchodilators with different mechanisms of action, administered via the same inhaler allow a higher efficacy not only owing to the optimization of bronchodilation linked to a synergistic effect.
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The study on intercation between aclidinium and formoterol, in particular, has shown a synergistic interaction that induces a fast effect onset after only 5 minutes after administration (p < 0.001) and from 120 to 240 minutes after administration (p < 0.05) and an addictive interaction in the time interval of 30 to 60 minutes after administration. Compared to the effect of single components, the FDC induced a synergistic effect with a variation in FEV1 of +55.14 ± 14.34% after 5 minutes and a +32.86 ± 15.73% between 120 to 240 minutes after administration. The results of this study shows that the combination aclidinium/formoterol produces a synergistic interaction both ex vivo in human bronchi studies where it induced the airways smooth muscle relaxation and in vivo in COPD patients with an increase in FEV1. The synergistic effect plays an important role in the clinical management of COPD, because it allows the optimization of bronchodilation combining low doses of drugs with different mechanisms of action.

This FDC has to be administered twice daily and this allows the symptoms control in the first morning hours, thus preserving a good quality of life (QoL) of patients, owing to the rapid improvement of FEV1, after the third hour of administration. The effectiveness of the single components, but also in the name of a possible enhancement in therapeutic adherence deriving from a simplification in therapy. The pharmacological mechanism that supports an association of more bronchodilators is complex and has to be found in the mutual influences between the cholinergic and the adrenergic systems at pre- and post-synaptic level. This mechanism includes the activation of the β2-Adrenergic receptor (β2-AR) from β2-agonist agents and the blockade of M3 post-synaptic receptors mediated by anticholinergic agents.

The intracellular strictly interconneted cros-talk between β2-AR and muscarinic pathway is explains the synergistic effects on airways smooth muscle relaxation observed with the combination LABA/LAMA both in ex vivo human bronchi studies and in vivo in COPD patients. Among the available FDCs, the one between aclidinium bromide and formoterol fumarate administered via the single inhaler Genuair offer numerous advantages compared to single agents separately or simultaneously administered through different inhalers. Aclidinium bromide and formoterol fumarate act synergistically with a rapid onset of bronchodilation 5 minutes after administration.

![Figure 4. FEV1 improvement induced by aclidinium compared to tiotropium and placebo on the first day of administration (from Fuhr et al., 2012, mod.).](image)
A clinical dose-response study conducted in patients with stable moderate-severe COPD (n = 566) to evaluate efficacy, safety and pharmacokinetic of three different formoterol dosages (6, 12, e 18 μg) in association with aclidinium bromide 200 μg, in comparison to monotherapy with aclidinium bromide 200

**Figure 5.** ACCORD COPD 1 Study: improvement induced by aclidinium in nocturnal symptoms (from Kerwin et al., 2012 42, mod.).

**Figure 6.** ACCORD COPD 1 Study: improvement induced by aclidinium in morning symptoms (from Kerwin et al., 2012 42, mod.).

**p < 0.01, ***p < 0.001 vs placebo**

Frequency of each of the variables was scored daily as follows: 0 = Never, 1 = 1-2 times, 2 = 3-4 times

***p < 0.001 vs placebo; *Severity of dyspnea was rated from 0 (none) to 4 (severe symptoms that interfered with normal activities); †Impact of breathlessness was rated from 0 (none) to 4 (severe symptoms that interfered greatly with morning activities).
and formoterol 12 μg or placebo has shown better improvements in respiratory parameters with the combination compared to monotherapies or placebo. The differences were significant for all the combinations compared to monotherapies and to placebo (p < 0.01) 49.

Efficacy and safety of aclidinium/formoterol FDC were evaluated in two wide clinical studies, ACLIFORM COPD study (ACLIdinium FORMoterol-COPD) 50 and AUGMENT COPD study (Aclidinium/formoterol flume rate combination for investigative use in the treatMent of moderate-to-severe COPD) 51.

As regards efficacy on lung functions, at week 24 aclidinium/formoterol 400/12 mg FDC has produced higher improvements in trough FEV1 from baseline values than placebo (least mean squares: 143 mL; p < 0.001), a clinically significant result because greater than 100 mL. The variation in trough FEV1 compared to formoterol was 85 mL at each timepoint (p < 0.001), which is in the range observed with different LABA/LAMA FDCs (70-95 mL) 50 51.

Aclidinium/formoterol 400/12 μg FDC significantly improved peak FEV1 by 334 mL vs placebo and single agents, with a bronchodilation onset within 5 minutes from first inhalation, statistically significant compared to placebo and to aclidinium (p < 0.05) and similar to formoterol 50 51.

Aclidinium/formoterol FDC showed a significant efficacy also in dispnoea (TDI) and QoL (SGRQ). Aclidinium/formoterol 400/12 μg induced a long lasting improvement in TDI of 1.4 units compared to placebo (p < 0.01) which is beyond the clinically significant threshold. (MCID > 1 unit). At 24 weeks, Aclidinium/formoterol 400/12 μg improved significantly the TDI by 0.4 units vs formoterol (p < 0.01) and by 0.44 units vs aclidinium (p < 0.05) 50 51.

The aggregated data analysis showed that FDC produces a clinically significant improvement in SGRQ of 4.4 units compared to placebo (p < 0.001) 50 51.

The efficacy of FDC on symptoms control during the whole day was evaluated through some questionnaires: the EXAcerbations of Chronic obstructive pulmonary disease Tool- Respiratory Symptoms (Exact-RS), the Early Morning Symptoms COPD (EMSCI) and the Nighttime Symptoms of COPD (NeSCI) questionnaire. Aclidinium/formoterol showed an improvement in daily COPD symptoms (dispnoea, cough, wheezing and sputum) compared to placebo, aclidinium and formoterol (p < 0.05) (evaluated with E.RS total score) 50 51.

The FDC produced an improvement in early morning symptoms vs placebo (p < 0.001), aclidinium (p < 0.001) and formoterol (p < 0.01) and in night symptoms vs placebo, aclidinium and formoterol (p < 0.05) 52 in COPD. The morning symptoms improvement implies a lesser limitation in daily activities. Aclidinium/formoterol was more effective compared to monotherapies in terms of dispnoea, morning and night symptoms severity and limitation in daily activities also in less symptomatic patients 53.

In a post hoc analysis of registative trials, aclidinium/formoterol FDC significantly reduced by 29% moderate and severe exacerbations compared to placebo (p < 0.05) 52.

In the AFFIRM study, in which aclidinium/formoterol and Fluticasone/Salmeterol (Flu/Salm) FDCs were compared in a non inferiority secondary endpoint, the LABA/LAMA FDC 400/12 μg produced an improvement in exacerbation rate similar to Flu/Salm (37.8% and 39.5% respectively) 54.

A crucial aspect in the efficacy of inhalatory therapy is the device used. A systematic review of letterature data showed that a lot of patients don’t use properly their inhaler due to a miscorrect inhalatory manuevre 55. It is thus necessary not only to develop new inhalers but also to favour an easiness of their use, especially in particular populations of patients, such as the elderly 56.

The recently developed Genuair® inhaler has peculiar technological innovations that improve both performance and safety. The use of the Genuair® inhaler was associated with a patients preference (percentage of patients: 79.1% vs 20.9%; p < 0.0001) and an overall satisfaction significantly greater compared to HandiHaler® 57.

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The percentage of patients that made one or more critical error in the device use was significantly lower with Genuair® than with HandiHaler (2.9% vs 19%; p < 0.0001) 58.

The Genuair® inhaler is also preferred by patients compared to Breezhaler® (percentage of patients: 72.7% vs 27.3%; p < 0.0001), with a greater satisfaction (mean score 5.9 vs 5.3; p < 0.0001). A lower number of critical errors was observed with Genuair® (2.4%) vs Breezhaler® (6.5%) 58.

The Genuair® inhaler was considered more practical and easy to handle: in a population of 626 elderly patients, 90% favoured the device after reading the patient information leaflet. This percentage increased to 96% among the patients who already used an inhaler and was 91% among patients with hand arthritis 59.

CONCLUSIONS

COPD is a heterogeneous and complex disease that affect mainly the elderly, representing one of the most prominent problem globally in health care systems, owing to the progressive ageing of the population. COPD exacerbations implicate the heavier socio-economic burden of this disease.
Frequent exacerbators have higher mortality rate, a worse QoL, and a faster decline in pulmonary function compared to non-frequent exacerbators. Exacerbations are associated with an increased airflow and systemic inflammation and with patho-physiological alterations that cause hypopinflation. This episodes that characterize COPD in an heterogeneous fashion are related to viral and bacterial infections accountable of a worsening of the inflammation. It is thus of paramount importance to delay the most that is possible the exacerbation onset, guaranteeing to the patient a good symptoms control during the whole day, allowing him to stay active and counteracting the vicious circle that from dispnoea leads to reduced exercise capability and to the muscle deconditioning with a worsening of QoL. An effective, rapid onset and long lasting bronchodilatation such as the one obtained with aclidinium bromide as monotherapy and more as fixed dose combination with formoterol can be a valid pharmacologic help to give an adequate answer to the unmet patient need still there nowadays.

References
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