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ORIGINAL

Triple inhaled therapy of formoterol/glycopyrrolate/budesonide reduces the use of oral corticosteroids and antibiotics during COPD exacerbations in real-world conditions

A. Calderón-Montero[a,*], J. de Miguel Diez[b], R. de Simón Gutiérrez[c], S. Campos Téllez[d], A.D. Chacón Moreno[e], R. Alonso Avilés[f], N. González Alonso[a], A. Montero Solís[g], D. Escribano Pardo[h], on behalf of APyC group[◊]

[a] *Family Physician, Cerro del Aire Primary Care Health Center, Majadahonda, Madrid, Spain*
[b] *Pneumologist, Gregorio Marañon Hospital, Madrid, Spain*
[c] *Family Physician, Luis Vives Primary Care Health Center, Alcalá de Henares, Madrid, Spain*
[d] *Pneumologist, Gomez Ulla Hospital, Madrid, Spain*
[e] *Internist, Guadalajara Hospital, Guadalajara, Castilla La Mancha, Spain*
[f] *Emergency department, Valladolid Clinic Hospital, Valladolid, Castilla y León, Spain*
[g] *Family Physician, Canal de Panama Primary Care Health Center, Madrid, Spain*
[h] *Delicias Sur Primary Care Health Center, Zaragoza, Aragón, Spain*

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KEYWORDS
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Abstract
Introduction: Triple inhaled therapy (TT) in one device has been shown in clinical trials to reduce exacerbations and in some cases mortality compared to dual inhaled therapy (DT) in one device in the population of moderate to very severe COPD patients and previous exacerbations. This evidence must be contrasted in real-world conditions.
Patients and methods: Non-intervention retrospective cohort study comparing the incidence of moderate and severe exacerbations in COPD patients treated with TT (formoterol, glycopyrrolate and budesonide, 5 mcg/72 mcg/320 mcg, $n = 112$) and DT (LAMA/LABA/ or LABA/inhaled glucocorticoid, $n = 107$) for 26 weeks under clinical practice conditions. Moderate exacerbations were evaluated by the use of oral corticosteroids and/or courses of oral antibiotics and/or attendance at the emergency room (<24 h) without hospitalization. Severe exacerbations were analyzed for hospitalizations for all causes, respiratory causes, cardiovascular causes, and pneumonia. Descriptive statistics for qualitative and quantitative variables, Chi square, Student's *t*-test and multivariate analysis were performed.

* Corresponding author.
E-mail address: acalderonmontero@gmail.com (A. Calderón-Montero).
◊ Please see a list of the members of the APyC group in Appendix A.

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Results: Both cohorts were homogeneous except for age (71.46 vs 66.65 TT vs DT, $p < 0.01$). TT reduced the use of oral corticosteroids by 42% (HR 0.58; 95%CI 0.41–0.82, $p < 0.01$) and the use of antibiotics by 25% (HR 0.75; 95%CI 0.60–0.94, $p < 0.01$). Hospitalizations due to respiratory causes were 11% lower in the TT cohort (HR 0.89; 95%CI 0.79–0.99, $p = 0.044$) with no difference in the incidence of pneumonia.
Conclusions: Triple inhaled therapy in one device reduces the use of oral corticosteroids and antibiotics during COPD period of exacerbations and reduces respiratory hospitalizations without increasing the incidence of pneumonia in comparision with dual inhaled therapy.

PALABRAS CLAVE
EPOC;
Triple terapia inhalada;
Doble terapia inhalada;
Vida real

La triple terapia inhalada de formoterol/glucopirronio/budesonida reduce el uso de corticoides orales y antibióticos durante las exacerbaciones de la EPOC en condiciones de vida real

Resumen
Introducción: Se ha demostrado en ensayos clínicos que la triple terapia inhalada (TT) reduce las exacerbaciones y la mortalidad en comparación con la doble terapia inhalada (DT) en la población de pacientes con EPOC de moderada a muy severa y exacerbaciones previas. Esta evidencia debe contrastarse en condiciones de práctica clínica.
Pacientes y métodos: Estudio de cohortes multicéntrico retrospectivo que compara la incidencia de exacerbaciones moderadas y graves en pacientes con EPOC tratados con TT (formoterol, glicopirrolato y budesonida, 5 μg/72 μg/320 μg/, n = 112) y DT (LAMA/LABA o LABA/glucocorticoide inhalado, n = 107) en la práctica clínica. Para las exacerbaciones moderadas se comparó el uso de corticosteroides orales y/o ciclos de antibióticos orales y/o asistencia a urgencias (< 24 h) sin hospitalización entre ambos grupos. Para las exacerbaciones severas se compararon las hospitalizaciones por todas las causas, por causas respiratorias, por causas cardiovasculares y neumonías. Se realizó estadística descriptiva para variables cualitativas y cuantitativas, chi cuadrado, prueba t de Student y análisis multivariante.
Resultados: Ambas cohortes fueron homogéneas, excepto por la edad (71,46 vs 66,65 TT vs DT, p < 0,01). La TT redujo el uso de ciclos de corticosteroides orales en un 42% (RR: 0,58; IC 95%: 0,41-0,82; p < 0,01) y el uso de antibióticos en un 25% (RR: 0,75; IC 95%: 0,60-0,94; p < 0,01). Las hospitalizaciones por causas respiratorias fueron un 11% menores en la cohorte TT (RR: 0,89; IC 95%: 0,79-0,99; p = 0,044), sin diferencias en la incidencia de neumonías.
Conclusiones: La triple terapia inhalada en un solo dispositivo reduce el uso de corticosteroides orales y antibióticos durante el período de exacerbaciones de la EPOC y reduce las hospitalizaciones respiratorias sin aumentar la incidencia de neumonías en comparación con la doble terapia inhalada.

Background

Randomized clinical trials (RCTs) constitute the highest level of scientific evidence and are the cornerstone of clinical practice guideline recommendations. Dual inhaled therapy (DT) has been shown in the past to reduce exacerbations and improve quality of life in patients with chronic obstructive pulmonary disease (COPD).[1–3] More recently, triple inhaled therapy (TT) in a single device with LAMA/LABA/IC (long-acting inhaled antimuscarinics/long-acting beta-2-adrenergics/inhaled corticosteroids) has gone a step further by reducing exacerbations and improving lung function compared to dual therapy[4–6] in the population of patients with moderate to very severe COPD and previous exacerbations, as well as in some of the studies decreasing all-cause mortality[5,6] and suggesting a possible benefit in cardiovascular mortality.[6]

As RCTs have a specific methodology, real-world studies are essential to confirm their benefits in the general population. Due to the greater heterogeneity of the COPD patient population under clinical practice conditions, studies sometimes show divergent results depending on the populations selected. In one study in a British population, TT only reduces exacerbations in patients with two or more

previous exacerbations.[7] In contrast, another study in a North American population found that early implementation of TT reduces the incidence of new exacerbations.[8] Other studies suggest that TT improves quality of life and lung function[9] and is cost-effective when used in a single device.[10] Additionally, and from a quantitative point of view, most exacerbations in clinical practice conditions are moderate.[11]

To verify the real-world benefits of TT, we designed an multicenter observational retrospective cohort study with the primary objective of analyzing whether TT is more effective than DT in reducing moderate exacerbations (outpatient cycles of corticosteroids and/or outpatient cycles of antibiotics and/or attendance at the emergency room without hospitalization). As secondary objectives, the incidence of severe exacerbations (hospitalizations) and pneumonia was compared between both groups.

Methods

Study design

This was a multicenter observational retrospective cohort study, conducted in Spain, of 26 weeks duration under clinical practice conditions. The patients came from primary care and outpatient pulmonology consultations. The cohorts were patients diagnosed with COPD on pre-treatment with TT (formoterol fumarate/dehydrate glycopyrronium/budesonide, 10 μg/14.4 μg/320 μg) compared with patients diagnosed with COPD on dual inhaled therapy (LABA/LAMA or LABA/IC). Treatments had been prescribed prior to patient selection under clinical practice conditions according to the indications in force in Spain as of June 1, 2022.

Patients and procedures

Patients were included in a 1:1 ratio for the cohort on TT and DT treatment, respectively if they met the selection criteria on November 1, 2022. The information for each patient was collected in their clinical records between November 1, 2022, and April 30, 2023, the termination date. The follow-up period was defined between the dates mentioned as this is the time with the highest probability of COPD exacerbations.

Selection criteria were adults older than 40 years, diagnosed with COPD (FEV_1/FVC < 70%) since at least three years before, on stable treatment with TT in a single device (formoterol fumarate/dehydrate glycopyrronium//budesonide 10 μg/14.4 μg/320 μg) or DT (LAMA/LABA or LABA/CI in a single or multiple devices) in the four months prior to patient selection (November 1, 2022) and classified with a COPD grade from moderate (FEV_1 < 80%) to very severe (FEV_1 < 30%). After reviewing patients diagnosed with COPD, all those who met the previous selection criteria were included in a 1:1 ratio for TT and DT respectively. As this was a study under clinical practice conditions, only a diagnosis of asthma and circumstances that made follow-up unfeasible, such as severe illness, displaced patients and immobile patients, were considered as exclusion criteria.

Study variables

To analyze the characteristics of the sample and the respective cohorts, socio-demographic and clinical variables were collected at the baseline visit and are presented in Table 1.

To assess the effect of TT compared to DT regarding the primary objective of moderate exacerbations, the incidence was compared as a percentage of patients with at least one event of each of the variables (outpatient cycles of corticosteroids, outpatient cycles of antibiotics, and attendance at the emergency room without hospitalization). To evaluate the effect of TT compared to DT on severe exacerbations, the incidence of all-cause hospitalizations, respiratory hospitalizations, cardiovascular hospitalizations, and incidence of pneumonia were compared between both groups. For each variable analyzed, it was considered positive if the patient had the event at least once between November 1, 2022 and April 30, 2023. For moderate exacerbations, records from the clinical history and reports of emergency care hospitals were used. For the diagnosis of pneumonia, a positive radiology or a specific clinical report was assessed. Discharge clinical reports were used to diagnose and classify hospitalizations.

Table 1 Variables collected at the selection visit.

Non-specific respiratory variables	Specific respiratory variables
Age	FEV_1
Gender	mMRC
Race	CAT
Heart failure	GOLD Assessment toll (A, B, E)
Myocardial ischemia	COPD diagnosis (years)
Atrial fibrillation	Previous year exacerbations
Peripheral arterial disease	Previous pneumologist visits in last year
Cardiovascular drugs	Previous Primary Care visits in last year
Pulmonary hypertension	Previous emergency visits in last year
Renal function	Smoking (current, former, never)
	Inhaled treatment (TT, LAMA + LABA, LABA + IC)

Abbreviations: FEV_1: forced expiratory volume in the first second. mMRC: modified Medical Research Council scale. CAT: COPD Assessment Test. GOLD: Global Initiative for Chronic Obstructive Lung Disease. TT: triple inhaled therapy. LAMA: long-acting inhaled antimuscarinic drugs. LABA: long-acting beta-2 adrenergics. IC: inhaled corticosteroids.

Additional specific information on changes in inhaled therapy, and use of short-acting bronchodilators, as well as changes in respiratory or cardiovascular treatments if any, was also obtained as of April 30, 2023.

Statistical analysis

Qualitative statistics, measures of centralisation with standard deviation, Chi-square test for comparison of qualitative variables and Student's t-test for independent samples for quantitative variables were used to analyze the descriptive sample and comparison of the cohorts in TT and DT.

As this was a retrospective study under clinical practice conditions in which patients were selected according to met the selection criteria, the sample size was not calculated a priori. The power of the study for the comparison of two proportions with an alpha significance level of 0.05 was estimated a posteriori for the main variables, being greater than 80% in all cases (83% for the antibiotic cycles and 91% for the oral corticosteroids cycles).

For the comparison between TT and DT of the variables of moderate and severe exacerbations and pneumonia, the Chi square test was used for a significance level of $p < 0.05$. Multivariate analysis techniques were used to evaluate the robustness of the effect. Age, GOLD classification, cardiovascular comorbidity, previous exacerbations, previous corticosteroid treatments, and previous antibiotic treatments were used as confusion variables

Analysis was predefined for the subgroups of age ≥ 65 and <65 years, gender, previous exacerbations, COPD type according to GOLD assessment tool, previous cardiovascular disease and tobacco use. For the analysis by subgroups and secondary variables, we used comparison of proportions statistics and Student's *t*-test for quantitative variables.

Ethical considerations

The study was conducted in accordance with the standards of good clinical practice for retrospective cohort studies in real-life and non-interventional conditions, as well as the declaration of Helsinki. The study does not have any intervention or follow-up of patients, obtaining data from the medical records after informed consent given by the patients. Both the information obtained from the clinical history and the data processing were carried out in an anonymized manner. The protocol was positively evaluated by local experts.

Study funding

To carry out the study, the authors declare that no public or private funding or grants has been received.

Results

Sample characteristics

The total sample consisted of 219 individuals, distributed as follows: 112 in the TT cohort and 107 in the DT cohort.

Table 2 Comparison of sociodemographic and clinical characteristics of the follow-up cohorts.

Variable	Triple-inhaled therapy	Dual-inhaled therapy	*p*
Age	71.46 ± 9.35	66.65 ± 10.28	0.001
Men (%)	64.5	66.4	0.774
FEV_1	52.93 ± 14.03	51.22 ± 13.63	0.593
CAT	18.74 ± 6.44	18.12 ± 9.41	0.648
mMRC	2.23 ± 0.98	2.08 ± 1.08	0.35
GOLD assessment tool (%)			
A	1.1	2.4	0.346
B	33.7	42.9	
E	65.2	54.7	
Body mass index	31.57 ± 4.99	31.18 ± 6.82	0.788
Last year previous exacerbations (% of patients)	83.5	74.5	0.144
Treatment at inclusion (TT/LAMA + LABA/LABA + IC) (n)	112/0/0	0/88/19	NA
Race (caucasin/hispanic/others) (%)	86.8/10.4/2.8	84.8/12.3/2.9	0.384
Smoking (current/former/never) (%)	43.4/34.9/21.7	46.2/35.5/18.3	0.831
Heart failure (%)	17.9	15.4	0.865
Myocardial ischemia (%)	9.6	5.8	0.307
Atrial fibrillation (%)	12.3	15.1	0.549
Albumin creatin ratio (mg/g)	27.67	15.27	0.659
Pulmonary hypertension	5.7	4.7	0.733
Primary care respiratory last year visits ($\geq$1) (% of patients)	86	80.3	0.229
Primary care cardiovascular last year visits ($\geq$1) (% of patients)	58.8	51	0.274

Abbreviations: FEV_1: forced expiratory volume in the first second. CAT: COPD Assessment Test. mMRC: modified Medical Research Council scale. GOLD: Global Initiative for Chronic Obstructive Lung Disease. BMI: body mass index. TTI: triple therapy inhaled. LAMA: long-acting inhaled antimuscarinic drugs. LABA: long-acting beta-2 adrenergics. IC: inhaled corticosteroids. MAP: primary care physician. Quantitative variables are expressed as mean $\pm$ standard deviation and qualitative variables as percentages.

Table 3 Analysis of the primary objective (moderate exacerbations) and secondary objectives (severe exacerbations and pneumonia as an adverse effect).

Variables	Triple-inhaled therapy	Dual-inhaled therapy	Hazard ratio 95%CI	*p*
Primary end-point				
Oral corticosteroids treatment (%)	31.3	53.9	0.58 (0.41–0.82)	0.001
Antibiotic therapy (%)	53.9	72	0.75 (0.60–0.94)	0.008
Emergency department attendance without hospitalitation (%)	34.7	46.3	0.75 (0.60-1.04)	0.096
Secondary end-point				
All-cause hospitalitations (%)	25.9	37.4	0.82 (0.52–1.28)	0.313
Respiratory hospitalitations (%)	20.5	29.9	0.89 (0.79–0.99)	0.044
Cardiovaacular hospitalitations (%)	2.7	4.6	0.93 (0.74–1.12)	0.168
Pneumonia (%)	3.6	2.8	1.12 (0.87–1.37)	0.47

The difference of five fewer patients in the DT cohort was because two patients were excluded due essential data were not available and three were not included in the analysis because they switched to open triple therapy. 100% of the patients in the TT cohort and 94% of the DT cohort used a single device.

Table 2 describes the different socio-demographic and clinical variables. Comparison between the two cohorts showed no differences except for age, which was higher in the TT cohort (71.46 ± 9.35 vs 66.65 ± 10.28, $p < 0.01$). Regarding clinical characteristics, patients were predominantly included in grade E (GOLD 2024), with predominantly moderate FEV_1 (52% and 51% for TT and DT respectively) and with a percentage of previous exacerbations of 83.5% and 74.5% for TT and DT respectively ($p = 0.114$). In the DT cohort, the most frequent therapy was LABA/LAMA (88%).

Outcome variables

In the analysis of the main objective, TT compared to DT reduced the risk of receiving oral corticosteroid treatment by 42% (HR 0.58, 95%CI 0.41–0.82, $p < 0.01$) and the risk of receiving antibiotic treatment by 25% (HR 0.75; 95%CI 0.60–0.94, $p < 0.01$) (Table 3). The TT also showed a trend toward lower emergency department attendance of 25% ($p = 0.096$).

Regarding the secondary objectives, TT showed a 11% reduction in the number of hospitalizations due to respiratory causes compared to DT (HR 0.89; 95%CI 0.79–0.99, $p = 0.044$) as well as a non-significant decrease 7% in hospitalizations due to cardiovascular causes (Table 3). No statistically significant differences were observed in all-cause hospitalizations, although the trend was in favor of TT with a risk reduction of 18%. There was no difference in hospitalizations for other causes.

To evaluate the effect of TT on moderate exacerbations depending on the type of DT, an exploratory analysis was performed comparing TT versus patients with LAMA/LABA, which showed statistically significant results very similar to those of the global sample (reduction of 39% in corticosteroid cycles and 26% in the use of antibiotic cycles).

In the predefined subgroup analysis for both corticosteroid and antibiotic treatment courses (Table 4), the benefits of TT compared to DT remain constant and homogeneous between B and E types specifically. In the comparison between B and E types, no differences were found in the effect according to age or clinical characteristics of the patients, as well as for the previous exacerbation profile. For exacerbator type A, the number of patients included was small, so the homogeneity of the result is less consistent.

In the multivariate analysis with the dependent variable of moderate exacerbations, type of treatment, sex, gender, previous exacerbations, COPD stage, smoke status, cardiovascular history, previous use of corticosteroids and previous use of antibiotics were included as independent variables. The adjusted logistic regression model was significant for prior exacerbations (beta coefficient 1.55) and type of treatment (beta coefficient 2.87).

With reference to adverse effects related to inhaled therapy, the incidence of pneumonias was similar in both groups ($n = 4$ and $n = 3$ for TT and DT respectively, $p = 0.607$). In the case of TT, one pneumonia was treated outside the hospital and three required hospitalization, while in DT, the three cases were hospitalized. There were no discontinuations of inhaled treatments in both cohorts.

Discussion

Optimize treatment of bronchodilator therapy in COPD patients is a need that should be shared by the primary care physician, the pulmonologist and all specialists treating these patients. In our study, triple inhaled therapy in a single device (formoterol fumarate dihydrate glycopyrronium/budesonide 10 μg/14.4 μg/320 μg) significantly reduces the need for oral corticosteroid treatment and antibiotic treatment and reduce respiratory hospitalizations during COPD exacerbations without increasing the incidence of pneumonia compared to inhaled double therapy under real-world conditions.

Prospective non-intervention studies in real-world conditions comparing the effectiveness of TT with DT in COPD patients are scarce. In a large retrospective cohort study in the UK primary care setting, TT reduced the risk of exacerbations by 13% and the incidence of an acute respiratory event by 26% compared to LAMA/LABA alone.[12] In a prospective study in primary care with 256 patients in which TT was initiated in patients with poorly controlled with DT, a 57.4% and 27.3% reduction in moderate and severe exacer-

Table 4 Subgroup analysis of the variables corticosteroid courses (A) and antibiotic treatment courses (B). Data are expressed as percentages.

(A)			
Variables	Triple-inhaled therapy ($n = 112$)	Dual-inhaled therapy ($n = 107$)	p
Age			
≥65 years	36.8	63.2	0.618
<65 years	28.6	71.4	
Gender			
Male	25	75	0.104
Female	50	50	
GOLD assessment tool			
A	100	0	0.386
B	33.3	66.7	
E	33.3	66.7	
Smoker			
Current	38.9	61.1	0.549
Former	0	100	
Never	33.3	66.7	
Cardiovascular disease			
Yes	25	75	0.427
No	37.9	62.1	
Previous exacerbations			
Yes	34.1	65.9	0.437
No	40.5	59.5	

(B)			
Variables	Triple-inhaled therapy ($n = 112$)	Dual-inhaled therapy ($n = 107$)	p
Age			
≥65 years	46.4	56.6	0.325
<65 years	31.3	68.7	
Gender			
Male	34.2	65.8	0.141
Female	52.650.0	47.4	
GOLD assessment tool			
A	0	0	0.655
B	33.3	66.7	
E	41.3	58.7	
Smoker			
Current	40	60	0.962
Former	44.4	55.6	
Never	39.3	60.7	
Cardiovascular disease			
Yes	35.3	64.7	0.662
No	41.5	58.5	
Previous exacerbations			
Yes	38.6	61.4	0.213
No	100	0	

bations, respectively, was found after 52 weeks of follow-up compared to previous exacerbations under DT.[13] Another large retrospective study from the USA shows that DT is associated with a 5% increase in the incidence of exacerbations for every 30-day delay in TT implementation.[9] Several studies by Suissa et al. show how TT in real-world conditions can reduce exacerbations in patients with severe or very severe COPD and a history of two or more exacerbations, but no benefit in patients with low or moderate COPD exacerbations.[14,15] Other studies also show less bene-

fit of TT in non-exacerbating patients.[16,17] It is interesting to note that in our study, 83% and 74% of the patients included in TT and DT respectively had a history of previous exacerbations, a common feature with the previously cited studies. As shown by multivariate analyses of our study, frequent previous exacerbations rather than COPD severity seem to be a determining factor in the effectiveness of TT compared to DT under clinical practice conditions.

Compared to DT, TT reduced the use of oral corticosteroids by 42% and the use of antibiotics during exacerbations by 25%. The results of the study by Voorham et al. also show a lower use of oral corticosteroids and antibiotics in patients treated with TT.[12] In a retrospective study in the UK, inadequate withdrawal of inhaled corticosteroids in patients on TT was associated with an increase in oral corticosteroid therapy compared to patients who remained on TT.[18] In our study, the benefits of TT was favorable overall and in the exploratory analysis also compared to the LAMA/LABA combination, which may be explained by the overall favorable effect on moderate exacerbations. As a consequence, given that a large proportion of moderate exacerbations are treated in primary care and in outpatient pulmonology consultations, it is relevant that triple inhaled therapy reduces the need for oral corticosteroid treatment. Overuse of antibiotics for exacerbations and respiratory infections can be a cause of multiple respiratory infections, as well as increasing healthcare costs.[19–21] Oral corticosteroid therapy to treat exacerbations increases the risk of lower respiratory tract infections and sepsis,[22] as well as the risk of hospitalization for pneumonia and all-cause mortality specifically when used for prolonged or repeated periods.[23]

Another relevant aspect of the benefits of TT in our study was the homogeneity of the results. Pre-specified analysis by subgroups showed that there were no differences regardless of the categories analyzed. This is important, as in addition to showing the consistency of the effect, it allows not having to specifically assess sociodemographic or clinical variables beyond the history of exacerbations as the main determinant of personalized treatment.

We did find a statistically significant lower frequency of respiratory hospitalizations compared to the DT cohort. Different studies and meta-analyses have shown that TT reduces the incidence of severe exacerbations (hospitalizations) in COPD patients,[24–26] which is compatible with the decrease in respiratory hospitalizations in our study. The incidence of pneumonia in clinical trials with inhaled triple therapy compared to DT has been similar or somewhat higher for TT.[4–6] In our study we did not find differences between TT and DT in the incidence of pneumonia, which may reflect that TT is safe under clinical practice conditions. In any case, the results should be taken with caution due to the low incidence of pneumonia and a follow-up period of 26 weeks.

Finally, it is important to note that all TT patients used a single device versus multiple devices. In the DT cohort, 94% of patients used a single device, so it cannot be assumed that the benefits of TT discussed above can be attributed solely to adherence. The use of single-device TT is a relevant factor given that 85% of patients using multiple devices are non-adherent,[27] only 24% maintain long-term treatment[28] and single-device use decreases exacerbations, mortality and resource use compared to multi-device TT.[29]

Strengths

The present study provides relevant information on the benefits of TT in clinical practice conditions. According to the clinical practice guidelines in COPD, the results of the present study can help both primary care physicians and pulmonologists to use TT in clinical practice conditions as well as to select those patients who can benefit most from it. It also provides relevant information on the benefits of TT on hospitalizations and its safety in clinical practice conditions.

Limitations

The study has some limitations that should be taken into account. Although both cohorts were comparable for most clinical and socio-demographic variables, the patients treated with TT were older. Being a non-interventional retrospective observational study under real-world conditions, the homogeneity of the cohorts cannot be pre-defined. However, we do not believe that this factor affects the results, considering that the main COPD severity variables were balanced. Also the sample size does not allow us to perform certain analyses on differences in the effect of TT compared to the two DT (LAMA/LABA or LABA/CI). However, most of the patients on double therapy were on LAMA/LABA (88%), and the exploratory analysis did not show differences for the largest LAMA/LABA subgroup. That is why we consider that the results can be extrapolated. to this therapy, which on the other hand is preferably indicated in the GOLD 2024 guidelines.[30] Finally, the results are for the formoterol fumarate/dehydrate glycopyrronium/budesonide (10 μg/14.4 μg/320 μg) formulation and therefore cannot necessarily be extrapolated to other single-device TT formulations.

Conclusions

This is a comparative observational retrospective study between two cohorts of inhaled therapy (triple therapy vs dual therapy) in real-world conditions that provides valuable information for the clinical practice of physicians treating COPD patients. Triple therapy in a single device (formoterol fumarate/dehydrate glycopyrronium/glycopyrronium/budesonide 10 μg/14.4 μg/320 μg) reduces the use of oral corticosteroid treatments and antibiotic treatments and respiratory hospitalizations during COPD exacerbations by 42%, 25% and 9% respectively compared to dual therapy. This may have implications for the optimization and personalization of treatment for patients with COPD.

Author's contribution

ACM, RdSG and SCT were responsible for the study design. ACM and SCT reviewed study data prepared and analyzed by an external agency. ACM and JdMD produced the first version

of the manuscript. All authors contributed and authorized the final version of the manuscript.

Study funding

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Conflict of interest

ACM has received financial compensation for conferences, studies, and advice from Glaxo, Astra Zeneca, FAES Farma, Viatris, Daicchi Sankyo. JdMD has received financial remuneration as a lecturer and advisor to GSK, FAES Farma, Astra Zeneca, Chiesi, Novartis and Pfizer. RdSG has received financial compensation as an advisor or lecturers from Glaxo, Chiesi, Astra Zeneca and Novartis.

Appendix A. APyC group

Alberto Calderon Montero (ACM), Family Physician. Cerro del Aire Primary Care Health Center. Majadahonda, Madrid, Spain. Javier de Miguel Díez (JdMD), Pneumologist. Gregorio Marañon Hospital, Madrid, Spain. Raúl de Simón Gutiérrez (RdSG), Family Physician. Luis Vives Primary Care Health Center, Alcalá de Henares, Madrid, Spain. Sergio Campos Téllez, Pneumologist. Gomez Ulla Hospital, Madrid. Spain. Raúl Alonso Avilés, Internist. Valladolid Clinic Hospital, Castilla y León, Spain. AndrésTenes Mayén. Sanitas Hospital. Madrid, Spain. Agustín Chacón Moreno. Internist. Guadalajara Hospital, Castilla La Mancha, Spain. Nuria González Alonso. Family Physician, Cerro del Aire Primary Care Health Center, Majadahonda, Madrid, Spain. Alicia Montero Solís, Family Physician, Canal de Panama Primary Care Health Center, Madrid. Spain. Daniel Escribano Pardo, Family Physician. Oliver Primary Care Health Center, Zaragoza, Aragón, Spain. Ana Pilar Javierre Miranda. Family Physician. Avenida de Aragón Primary Care Health Center, Madrid, Spain. Marta Cuevas Cortijo. Family Physician. Potosí Primary Care Health Center, Madrid, Spain. Jorge Rodriguez Reguera. Family Physician. Mar Báltico Primary Care Health Center, Madrid, Spain. Raúl Coleto Gutiérrez. Family Physician. Ramón y Cajal Hospital, Madrid, Spain. Vladimir Jiménez Gonzalez. Family Physician. Felipe II Primary Care Health Center, Madrid, Spain. Alejandra De Miguel Gordillo. Family Physician. SERMAS, Alcorcón, Madrid, Spain. Yolanda Bermejo Barbo. Family Physician. Presentación Sabio Primary Care Health Center, Madrid, Spain. Maria Fátima Bermejo Fernández. Family Physician. Torrelodones Primary Care Health Center, Torrelodones, Madrid, Spain. Luis Eduardo Alejos Ramirez. Family Physician. Humanes Primary Care Health Center, Humanes, Madrid, Spain

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