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Rapid Improvement of Symptom Scores and QoL on Short-Term with Extrafine Fixed Triple Inhaled Therapy and Patient Characteristics in Moderate COPD in a Real-Life Setting

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Abstract

Aim: There is a lack of knowledge of the efficacy of single inhaler triple combination therapy in patients with moderate COPD.

Subjects and Methods: RATIONALE is a 52-week, ongoing phase IV, multicentre, prospective clinical trial evaluating the efficacy of single inhaler triple therapy BDP/FF/GB in patients with moderate COPD. The main eligibility criteria were age ≥ 35 years, 50% ≤ FEV1 <80%, CAT score ≥ 10 or mMRC ≥ 2 and ≥ 2 exacerbations/year. Changes in the treatment of patients had to happen before and irrespective of study inclusion.

A pre-planned interim analysis of the first two visits was conducted 1 year after the start of the study.

Results: As of data cut-off (March 18th, 2021), 616 patients were enrolled in the study and 498 patients were included in this analysis. 91 patients (18.3%) had received ICS-LABA, 140 patients (28.1%) open triple combination and 267 (53.6%) patients LABA-LAMA as previous therapy. The proportion of patients not reporting cough/sputum production increased by 9.05% and 19.68%, respectively (p<0.0001). The proportion of patients not reporting any limitations increased in all EQ-5D-3L domains (p<0.0001). The average mMRC scores decreased significantly (p<0.0001). The mean values in the CAT and VAS scores improved in all FEV1 groups (p<0.0001).

Conclusion: In this interim analysis, significant improvements were seen in all of the assessed parameters, showing a clear benefit for extrafine single inhaler triple therapy use in patients with moderate COPD who were symptomatic on previous dual or open triple therapy.

Keywords: COPD; Fixed triple combination; Real-world study; Adherence; Symptom scores; Quality of life

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Introduction

COPD is one of the most common respiratory diseases and the third leading cause of mortality worldwide [1]. As a chronic, progressive disease, COPD is characterized by a slow deterioration of lung function and an increase in respiratory symptoms, such as breathlessness, chronic cough and sputum production. In many cases, the disease is interrupted by acute exacerbations, which are rapid, sometimes life-threatening worsening of symptoms. The goals of treatment are to reduce exacerbation risk, alleviate symptoms, increase Health-Related Quality of Life (HRQoL), and preserve lung function [2].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend initial and subsequent treatment based on the exacerbation risks and symptoms of patients, most prominently dyspnea. The GOLD guidelines recommend starting therapy with a Long-Acting Muscarinic Antagonist (LAMA), dual bronchodilator therapy (Long-Acting B2 Agonist (LABA)-LAMA) or Inhaled Corticosteroid (ICS)-LABA combination therapy. The fixed (single inhaler) triple combination of these three agents is suggested for patients with resistant symptoms and/

or frequent exacerbations, despite dual therapy [3]. Triple therapy has been proven to be the most effective treatment modality for these high-risk patients; however, some questions remain regarding its real-life efficacy and the exact patient populations that could benefit the most from treatment [4,5]. Furthermore, its superiority to open triple treatment is still debated.

The efficacy of fixed triple combinations had been assessed in several studies. Extrafine beclometasone, formoterol and glycopyrronium bromide (BDP/FOR/GB) [6] has been evaluated in three different studies-triple therapy was compared to a LAMA (TRINITY) [7], LAMA/LABA (TRIBUTE) [8] and ICS/LABA (TRILOGY) [9], with two studies having the same primary efficacy endpoint (moderate and severe exacerbation rates at week 52), while TRILOGY evaluated the change in pre- and post-dose forced expiratory volume in 1 second (FEV_1) and the level of breathlessness as co-primary endpoints. The efficacy of Fluticasone Furoate, Umeclidinium and Vilanterol (FF/UMEC/VI) [10] was assessed in two trials-one multi-arm study (IMPACT) [11] that compared a fixed triple combination against LAMA/LABA and ICS/LABA, with exacerbation rate (moderate or severe) at week 52 as the primary endpoint and FULFIL [12], which was a two-arm study that compared triple therapy against ICS-LABA, with the change in trough FEV_1 and the St. George Respiratory Questionnaire (SGRQ) as co-primary endpoints. Finally, Budesonide, Formoterol and Glycopyrronium bromide (B/FOR/GLY) [13] was assessed in two studies-one

24-week study (KRONOS) [14] that compared fixed dose triple therapy against LAMA/LABA and ICS/LABA, with

FEV_1 Area under the Curve in 0 h to 4 h (AUC_{0-4}) and change in pre-dose trough FEV_1 as primary endpoints and

ETHOS, which was a 52-week study that compared two different doses of triple therapy against LAMA/LABA and ICS/LABA, with the annual exacerbation rate as the primary endpoint [15].

All these studies reached their primary endpoints, providing evidence of improvement in many different outcome measures with triple therapy. Acknowledging these results, the GOLD guidelines from 2019 stated the following: "Triple inhaled therapy with ICS/LAMA/LABA improves lung function, symptoms and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA or LAMA Monotherapy (Evidence A)".

However, there still are some important patient populations where the benefits of triple therapy are less obvious. In TRILOGY, TRINITY and TRIBUTE, previous triple therapy was an exclusion criterion [7-9]. While the IMPACT, FULFIL, KRONOS and ETHOS studies allowed inclusion of these patients, only about one-third of the randomized subjects had received triple therapy beforehand (except for ETHOS, where this percentage reached 39%) [11,12,14,15]. Also, there is a lack of data comparing the efficacy of open (with two or more inhalers) *vs.* fixed triple therapy.

Another important gap in our current knowledge is the efficacy of triple therapy in patients with moderate COPD (50 ≤ FEV_1 <80%). The Trimbow studies evaluated patients with severe airflow limitations only and even though the IMPACT, FULFIL and ETHOS studies allowed the inclusion of patients with moderate COPD (but only with a high exacerbation risk), the mean FEV_1 of both study populations were below 50% [11,12,15]. In KRONOS, almost half of all included patients had moderate airflow limitation (average FEV_1 not provided); however, changes in COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) scores as a primary or secondary endpoint were not evaluated and changes in the St. George Respiratory Questionnaire (SGRQ) were only assessed as a secondary endpoint [14]. It is important to note that, even though the FEV_1 based COPD severity is the most important prognostic factor for mortality, it only weakly correlates with symptom severity, meaning that even patients with mild and moderate COPD may suffer from serious debilitating symptoms [3]. Moreover, since the 2017 GOLD update, FEV_1 does not affect ABCD group assessment and therapy choice [16]. Finally, it has already been proven that, even though mild and moderate patients have less extensive airway obstruction, lung remodeling and small airway disease is also already present in their lungs, with more than a 45% decrease in alveolar surface area. This could potentially cause severe symptoms and lead to the aggravation of lung tissue damage [17,18]. Based on the importance of small airway disease, authors have already suggested the possibility of earlier therapeutic intervention in mild and moderate COPD [17].

The goal of this prospective, non-interventional, multicentre study was to evaluate the adherence to treatment in patients with moderate airflow limitations (50% ≤ FEV1 <80%) on single inhaler triple combination therapy and investigate its efficacy on exacerbation rate, symptom control and quality of life as compared to their previous Treatments.

Methods

Study design

Our study was a multicentre, non-interventional, prospective study with 50 active study sites across Hungary. The diagnosis, treatment, inclusion and follow-up of patients were performed by pulmonology specialists. The enrolment of patients took place in dispensaries, outpatient clinics specializing in respiratory diseases and in outpatient departments of hospitals in all regions of Hungary. One interim analysis was pre-planned.

Patients attending regular ambulatory visits were screened, and if inclusion criteria were met, they were enrolled and followed for 52 weeks, with the second visit (the first visit being the one at study entry) 1 month after enrolment, the third visit at month 6 and the fourth visit at 1 year. The study was approved by the National Scientific and Research Ethics Committee of Hungary and was conducted according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. All patients provided written, informed consent before enrolment.

As study enrolment was halted by the COVID-19 pandemic, the pre-planned interim analysis of the first two visits (at enrolment and at 1 month) was conducted and data were analyzed regarding the secondary endpoints.

Patients

Eligible patients were all outpatients ≥ 35 years old who were diagnosed by a respiratory specialist with COPD for more than 1 year and had a post-bronchodilator 50% ≤ FEV1 <80%. As well as a ratio of FEV_1 to forced vital capacity of <0.7. Patients had to be symptomatic, with a mMRC score of at least 2 or a CAT score of at least 10 and had at least one severe (requiring hospitalization) or two moderate exacerbations in 12 months (as part of the GOLD group assessment at any time in the patient's history, not necessarily before study enrolment). Patients were eligible if the treating physician decided

Table 1: All inclusion and exclusion criteria.

Inclusion criteria
Specialist diagnosed COPD for more than 1 year
35 years of age or older
Ambulatory patient
Symptomatic patient (CAT ≥ 10 OR mMRC ≥ 2)
FEV1 ≥ 50% at inclusion
Patient is capable of providing consent
Frequent exacerbator phenotype (Severe ≥ 1 or moderate exacerbations ≥ 2 in 12 months at any time in the patients' history)
Patients' treatment is changed to fix triple combination irrespective of and prior to trial entry
Exclusion criteria
Patient is incapable of completing study questionnaires
Patient does not provide consent for data collection
Having a diagnosed but untreated chronic condition
Continuous, maintenance oral corticosteroid treatment
Diagnosis of asthma
Active exacerbation at the time of screening
Acute exacerbation in the 4 weeks previous of screening
Malignant disease affecting the quality of life

to switch therapy before and irrespective of study entry from LABA/LAMA, ICS/LABA or from open triple combination (ICS/LABA/LAMA in more than one device) to single inhaler triple therapy.

Key exclusion criteria were asthma diagnosis, ongoing oral corticosteroid treatment, acute exacerbation in the previous 4 weeks and active malignant disease affecting quality of life. All eligibility criteria are listed in Table 1.

Procedures

If patients were eligible and gave consent for study inclusion, baseline data were collected on spirometry, exacerbation history in the previous 12 months, symptom severity (CAT and mMRC scores, as well as frequency and severity of cough and sputum production) and physiological parameters, such as arterial Oxygen Saturation (SpO2), Blood Pressure (BP), Heart Rate (HR), weight, height and calculated Body Mass Index (BMI) derived from the previous two parameters. Cough and sputum production were assessed in depth by recording the severity on a subjective scale of 1 to 10 (10 being the worst), diurnal frequency variation and whether it is provoked by exercise or not. The following data were also recorded: Level of education, inhaler technique, previous medication (before switching to fixed dose triple therapy), smoking status and history and quality of life measured by the internationally approved EuroQoL (EQ-5D-3L) questionnaire. This tool consists of five questions for different domains of quality of life (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) to which patients can rate their wellbeing on three levels (no problems or moderate or severe problems) by ticking the box next to the choice that best describes their health status. This choice can be 'translated' into one number (scale of 1-3) and the numbers chosen for the five dimensions can be combined into a 5-digit number that describes the patient's health state. Also, patients were required to quantify their general wellbeing on a vertical Visual Analogue Scale (VAS), with 0 being the worst and 100 the best imaginable health state.

During the 52 weeks of the study, patients attended visits at weeks 4, 24 and 52, where data on symptoms, exacerbations, BP, HR, SpO2, quality of life measures and current medication were recorded. On the last visit, data on comorbidities and smoking status were also collected. All adverse events, related to treatment were also recorded. At study inclusion, patients also gave consent for data collection from the National Health Insurance Fund (NHIF) database on prescriptions filled during the trial and the previous year, which was for the assessment of adherence to therapy. The Hungarian health care system is a comprehensive, compulsory national health insurance scheme, covering almost 100% of the Hungarian population. The NHIF database contains data on filled prescriptions for all the registered patients, so the evaluation of treatment adherence will be possible for all enrolled patients.

Outcomes

Our primary objective was to assess the adherence of patients to single inhaler triple combination therapy after 52 weeks and to assess the possible correlation of adherence to therapy and symptom severity (mMRC and CAT scores) on a countrywide level. The evaluation of adherence will be performed by evaluating the insurer's data on filled prescriptions, with permission from the NHIF, and the consent from each individual patient. As these data will only be available at the end of the study, the primary endpoint could not be analyzed at the interim analysis.

Secondary endpoints were changes from baseline in the EQ-5D-5L, mMRC and CAT scores recorded at each visit; rate of moderate and severe exacerbations over 52 weeks; change in adherence to therapy compared to the previous therapy in the year preceding study inclusion; change in adherence to therapy based on the type of previous therapy (ICS-LABA/LABA-LAMA/open triple) and change from baseline in pre-dose FEV_1 to week 52. Also, a secondary objective was to assess the effect of switching to extrafine drug formulation in the subgroup of patients, previously not on extrafine inhaled medication. Further objectives will be to assess the following characteristics of included patients at the end of the study: The physiological findings (as detailed earlier), socioeconomic status, and

Table 2: Baseline characteristics of patients and differences in proportions among therapy groups.

		Maintenance therapy before study enrolment			Number of patients	Overall p
		ICS/LABA	Open triple	LABA/LAMA		
Cough	No	1 (1.1%)	7 (5%)	6 (2.2%)	498	0.167
	Yes	90 (98.9%)	133 (95%)	261 (97.8%)		
Sputum	No	4 (4.4%)	20 (14.3%)	24 (9%)	498	0.0352*
	Yes	87 (95.6%)	120 (85.7%)	243 (91%)		
Severe exacerbations	None	70 (76.9%)	119 (85%)	220 (82.4%)	498	0.3026
	1	20 (22%)	17 (12.1%)	39 (14.6%)		
	2	1 (1.1%)	4 (2.9%)	4 (1.5%)		
	2<	0 (0%)	0 (0%)	4 (1.5%)		
Moderate exacerbations	None	10 (11%)	27 (19.3%)	56 (21%)	498	0.085
	1	7 (7.7%)	7 (5%)	36 (13.5%)		
	2	68 (74.7%)	97 (69.3%)	156 (58.4%)		
	2<	6 (6.6%)	9 (6.4%)	19 (7.1%)		
Reliever usage	No	12 (13.2%)	18 (12.9%)	55 (20.6%)	498	0.0771
	Yes	79 (86.8%)	122 (87.1%)	212 (79.4%)		

*indicate statistical significance

prevalence of comorbidities, spirometry findings and the effect of these factors on clinical outcomes.

Statistical analysis

Data collection and database management (Medical Research Agent® eCRF system) were conducted by Medisol Development Ltd. (Nemesvámos, Hungary); the statistical analysis was conducted by Adatrendező Ltd. (Dunaharaszti, Hungary). To compare baseline parameters, Analysis of Variance (ANOVA) and two-tailed t-test were performed for quantitative parameters, while for qualitative parameters, binomial logistic regression was used. For pairwise comparisons, Tukey's test was used. To compare differences between the first and second visits, McNemar's test was performed for qualitative parameters and the two-tailed t-test was used for quantitative parameters. When comparing changes between the first and second visit, among different groups, combined logistic and combined linear models were used (for qualitative and quantitative variables). Odds Ratios (ORs) were provided with 95% Confidence Intervals (CIs).

For statistical analysis, we used the open source Python 2.7.12 on a MAC operating system (Anaconda Inc., Austin, TX) and R for Windows 3.4.2 (R Core Team, https://www.R-project.org/).

Results

Patients

The study started on February 01st, 2020, with the first patient being enrolled on February 18th, 2020, and data collection for the interim analysis was performed on February 01st, 2021. During this time, 616 patients were enrolled, which was lower than the planned enrolment rate. This delay was due to the COVID-19 pandemic and countermeasures implemented for the mitigation of its effect, which forced severe limitations on outpatient care facilities, including prohibiting outpatient care during the first wave [19]. Also, due to exclusions and study incompletion, the data of only 498 patients were assessed. The steps and reasons for exclusion are shown in Figure 1.

In all, 52.4% of our patients were female, with a mean age was 64.6 years (95% CI: 63.81-65.43). Also, patients (53.6%) were active smokers and only 47 patients (9.4%) were non-smokers. Of the active and ex-smokers, 259 patients (38.2% of the whole population) smoked more than 30 pack-years; 340 patients (68.3%) were obese (BMI >25 kg/m^2), which is higher than the Hungarian average [20]. In all, 91 patients (18.3%) had received ICS/LABA, 140 patients (28.1%) had received open triple combination and 267 patients (53.6%) had received LABA/LAMA as previous therapy (therapy groups) before study inclusion. All baseline patient characteristics, in the three subgroups (dual bronchodilator therapy, ICS-LABA combination therapy and open triple combination) are shown in Table 2, 3. Overall p values represent the possible differences between the three studied populations (a p value of <0.05 is considered statistically significant).

There was a statistically significant difference among therapy groups in the proportion of patients reporting sputum production (p=0.035) and in average mMRC scores (p=0.0001). There was an overall statistically significant difference in the average CAT scores of the therapy groups (p<0.0001) as well. In the pairwise comparison, there was a statistically significant difference in the average mMRC scores of the ICS/LABA group as compared to those in the LAMA/LABA and open triple groups (2.69 *vs.* 2.42 and 2.35, respectively; p=0.0007 and 0.0001, respectively). There was also a statistically significant difference in the average CAT scores in the pairwise comparison-average CAT score 18.93 (LABA/LAMA) *vs.* 22.40 (ICS/LABA, p<0.0001) *vs.* 20.88 (open triple, p=0.0076), indicating that LAMA/LABA patients are generally in a better health condition, while ICS/LABA patients are in a more severe health condition in Hungarian outpatient units.

One of our goals was to measure how difficult it is for patients to learn the correct inhaler technique for a new device. Hence, we measured the time (in minutes) it takes for the healthcare personnel to explain to the patient the correct use of the device and verify that the patient actually understood the instructions, by checking the inhaler use technique of the patients. Interestingly, there was a statistically significant difference between the groups, with the patients of the ICS-LABA group requiring the most time to learn the correct inhaler technique compared to both other groups. The number of tries is defined as the number of attempts the patients

Table 3: Baseline characteristics of patients and differences of mean values among therapy groups.

		ICS/LABA	Open triple	LABA/LAMA	Total	Number of patients
Time to learn appropriate inhaler technique (minutes)	Mean	7.3	5.8	5.6	6	
	2.5% CI	6.5	5.2	5.2	5.7	
	97.5% CI	8.2	6.4	6	6.3	
	No. of patients	91	140	267	498	498
	Overall p	0.0001*				
No. of tries to learn appropriate inhaler technique	Mean	2.6	2.3	2.4	2.4	
	2.5% CI	2.3	2.1	2.3	2.3	
	97.5% CI	2.9	2.4	2.6	2.5	
	No. of patients	91	140	267	498	498
	Overall p	0.135				
modified Medical Research Council (mMRC) score	Mean	2.7	2.4	2.4	2.4	
	2.5% CI	2.6	2.3	2.4	2.4	
	97.5% CI	2.8	2.4	2.5	2.5	
	No. of patients	72	124	220	416	
	Overall p	0.0001*				
COPD Assessment Test (CAT) score	Mean	22.4	20.9	18.9	20.1	
	2.5% CI	20.7	19.9	18.3	19.6	
	97.5% CI	25.1	21.9	19.6	20.7	
	No. of patients	91	139	267	497	497
	Overall p	<0.0001*				

*indicate statistical significance

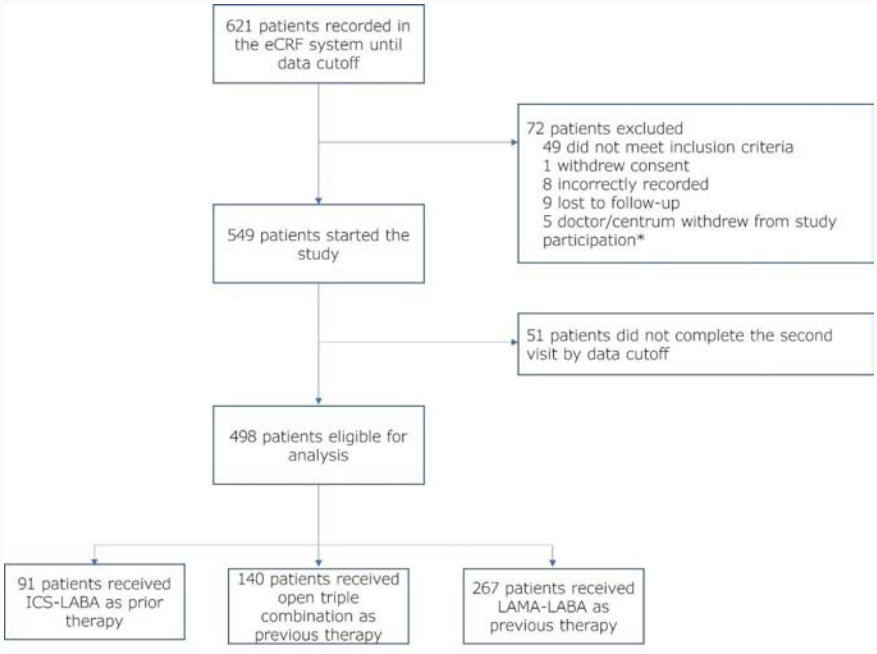

Figure 1: Study profile.
*Withdrawal from the study by doctors/study sites was due to earlier retirement or reallocation of medical personnel due to the COVID-19 pandemic.

had, until the healthcare professional considered their use of the inhaler correct. There was no statistically significant difference in this parameter among the groups.

Outcomes

As adherence will only be assessed at the end of the study, our primary endpoint could not be evaluated at the interim analysis.

Our main secondary endpoints were changes from baseline to the second visit in symptoms (CAT and mMRC scores and presence of cough and sputum production) and the EQ-5D-3L domains. Exacerbation rates could not be assessed due to the short period.

There were statistically significant improvements in all the assessed outcome measures. The proportion of patients experiencing

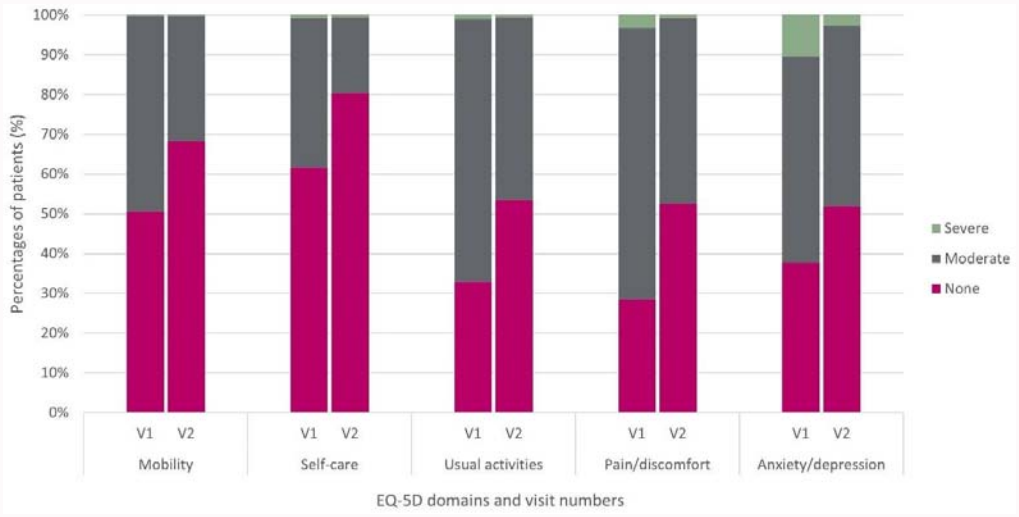

Figure 2: Patient distribution in EQ-5D-3L domains on visits 1 and 2.
V1: Visit 1; V2: Visit 2

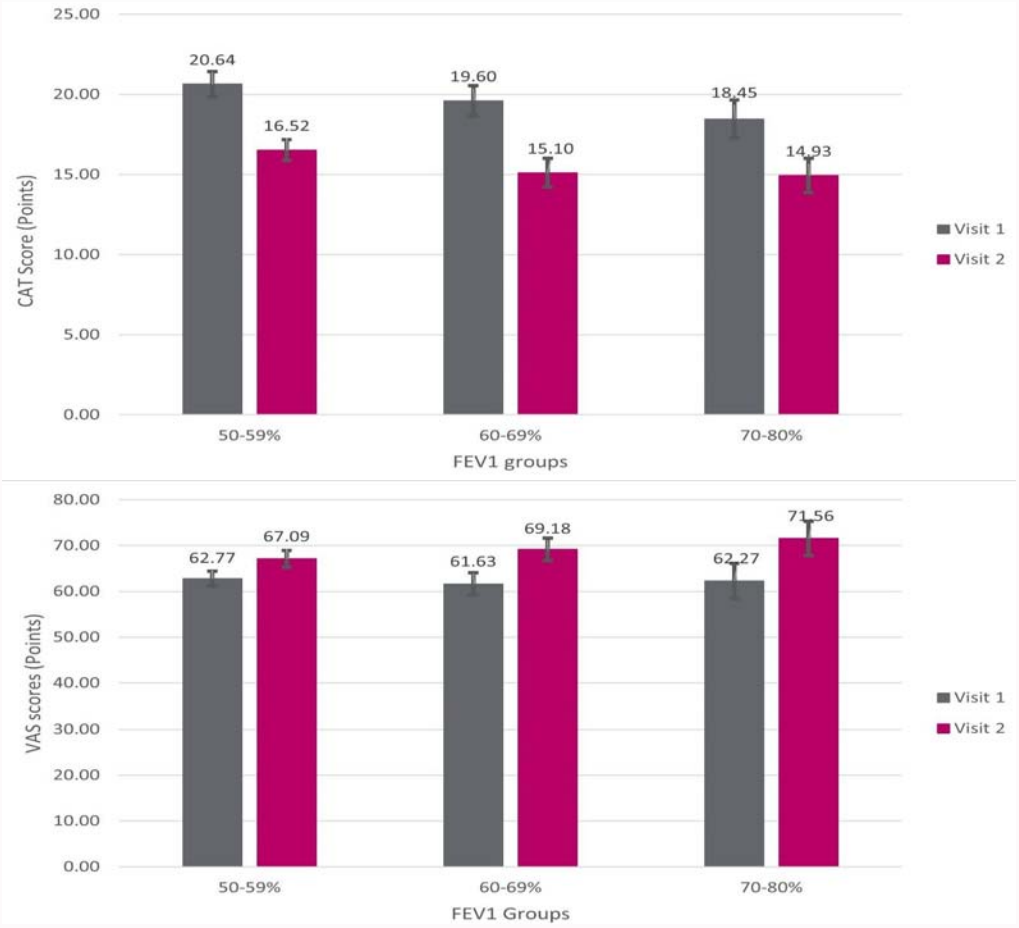

Figure 3: A and B. Average CAT (A) and VAS (B) scores in different FEV1 groups at visits 1 and 2.
V1: Visit 1; V2: Visit 2

chronic cough and sputum production decreased by 9.05% (45 patients) and 19.68% (98 patients), respectively. The proportion of patients not reporting any disability on the domains of the EQ-5D-3L questionnaire increased by 17.7% (88 patients-mobility), 18.7% (93 patients-self-care), 20.5% (102 patients-usual activities), 24.1% (120 patients-pain/discomfort) and 14.3% (71 patients anxiety/depression), respectively (Figure 2). The proportion of patients with normal SpO2 values (SpO2>95%) increased by 13.05% (65 patients). The average mMRC scores decreased significantly by 0.33 (95% CI: -0.38 to -0.28). The p-value in all cases was <0.0001.

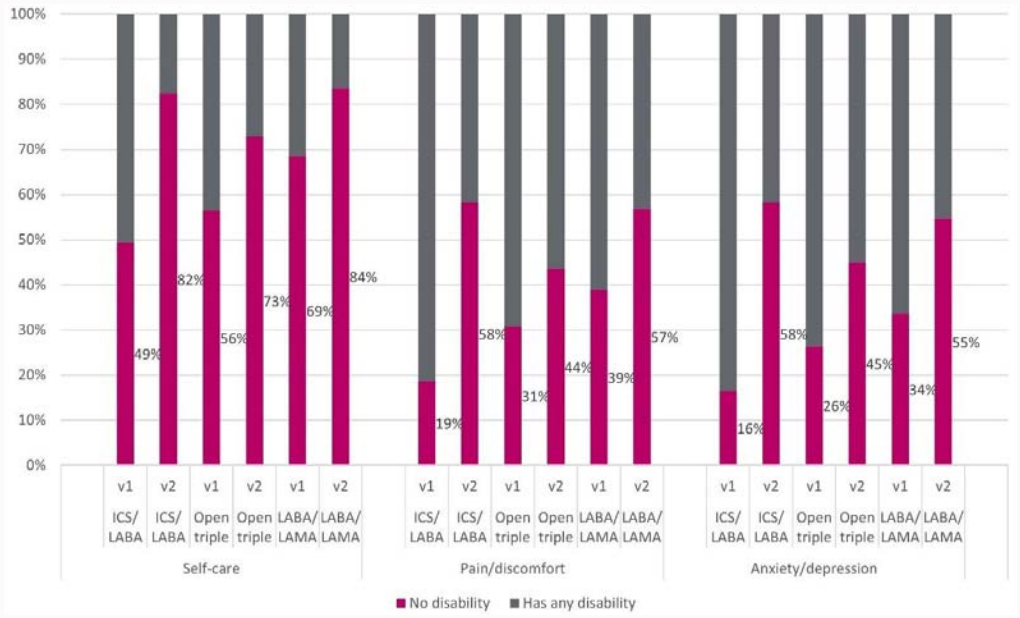

Figure 4: Proportion of patients who reported having any level of disability on self-Care, usual activities and pain/discomfort domains. V1: Visit 1; V2: Visit 2

To better understand the effect of fixed triple combination therapy in the patient group with $FEV_1 \geq 50\%$, we evaluated changes in the CAT and VAS scores in a more detailed manner. All patients were assigned to one of following three FEV_1 groups: 50% to 59% (FEV_1 Group 1), 60% to 69% (FEV_1 Group 2) and 70% to 79% (FEV_1 Group 3). In most groups, there was a statistically significant improvement in all three parameters. The mean value of the CAT score improved significantly in all three FEV_1 groups ($p<0.0001$ in all cases) and the largest numerical improvement was seen in Group 2 (mean CAT score change of -4.50). The mean change in VAS score also improved significantly in all three FEV_1 groups ($p<0.0001$ in all cases), but the largest numerical improvement was seen in Group 3 (average VAS score increase of 9.29). These changes are shown in Figure 3A, 3B.

Group comparisons

To further characterize the treatment effect, we evaluated the reported changes in the aforementioned parameters based on the previous therapy of the patients. From all parameters assessed, there were statistically significant improvements in sputum production ($p=0.0001$), average mMRC scores ($p<0.0001$) and all domains of the EQ-5D-3L questionnaire (mobility domain $p=0.0001$, anxiety/depression domain $p=0.0139$ and $p<0.0001$ for the remaining three domains) in the ICS/LABA group (n=91). There were statistically significant improvements in average CAT scores in Groups 1 and 2 (-6.47, -6.21; $p<0.0001$, respectively) but not in Group 3 (-1.53, $p=0.15$). There were also statistically significant improvements in the average VAS scores in Groups 2 and 3 (8.68, 14.07; $p=0.014$ and $p=0.0005$) but not in Group 1 (-3.94, $p=0.216$).

There were statistically significant improvements in cough, sputum production, SpO2 values, average mMRC scores and all domains of the EQ-5D-3L questionnaire in the LABA/LAMA group (all $p<0.0001$). The values of the CAT and VAS scores improved significantly in all FEV_1 (VAS score FEV_1 Group 3 $p=0.0147$; all other p values <0.0001). The highest improvements in the CAT and VAS scores were seen in FEV_1 Group 2 (-3.78 CAT and 7.95 VAS, respectively). In Group 3, there were no patients with an mMRC score higher than 2 on the second visit, so a formal analysis was not possible.

In the open triple group, there were statistically significant improvement in cough ($p=0.0013$), SpO2 ($p=0.010$) sputum production, average mMRC scores and all domains of the EQ-5D-3L questionnaire ($p<0.0001$ in all cases) in all FEV_1 groups. The average CAT and VAS scores improved significantly in all FEV_1 groups, with the largest numerical improvement seen in Group 3 (mean change of -6.22 and 12.90 in the CAT and VAS scores, respectively, $p=0.004$ and $p=0.015$).

We compared the differences in changes recorded between the first and second visits among the baseline therapy groups for further analysis. The most important differences were observed in the EQ-5D-3L domains of self-care, usual activities and pain/discomfort, where there was a significant interaction between baseline therapy and changes experienced between the first two visits. More specifically, the increase in the proportion of patients not reporting any disability in these domains increased the most in the ICS/LABA group and the least in the open triple group. The changes in proportion are shown in Figure 4.

Discussion

Our study showed that switching to single inhaler triple combination therapy in symptomatic patients with moderate COPD using ICS/LABA, LABA/LAMA or open triple combination therapy resulted in significant improvements in all assessed symptom scores and all dimensions of quality of life rapidly, even after one month of treatment. These results suggest that there is a significant patient population with moderate COPD whose symptoms are uncontrolled despite dual or open triple therapy and who could greatly and rapidly benefit from single inhaler triple therapy.

To put our results into perspective, the average decrease in the CAT score ranged from 3.52 to 4 in 1 month-both of which far exceed the Minimum Clinically Important Difference (MCID) of 2 or more points over 2 to 3 months [21].

As the current study was the result of an interim analysis, it is not possible (nor is it the goal of the current article to draw conclusions on long-term efficacy. However, the level of improvement seen in all dimensions is promising. Also, it is important to highlight that improvement was seen not just in patient-reported outcomes (which could be affected the most by study effect-the positive perception of study inclusion) but also in arterial oxygen saturation, which is an objective parameter of respiratory efficacy.

Another goal of our study was to characterize the moderate COPD population, which is not primarily treated with fixed dose triple combinations. In our study, the majority of patients were treated with dual bronchodilator therapy. Based on the differences in the CAT scores and exacerbation rates, we can conclude that patients treated with ICS/LABA were generally in worse health at enrolment. As the current Hungarian financial protocol still follows the GOLD guidelines before 2017, ICS/LABA is generally used for patients with more severe COPD [22]. This perception could also affect the treatment choice for patients with moderate airflow obstruction with a high symptom burden.

Another finding of our study was that patients with different levels of airflow obstruction (subgroups of the moderate group) experienced different levels of improvement in the CAT, EQ-5D-3L and VAS scores when switched to fixed triple inhaler therapy. Even though the parameters were self-reported and reflect on symptom severity or their effect on the quality of life, there was no clear tendency towards larger improvement in any certain FEV_1 subgroup. There were also some differences in improvement among the groups defined by baseline treatment; however, the comparison of these changes must be assessed with caution, as in some subgroups the number of patients was low (for example, FEV_1 Group 3 of the ICS/LABA group included only 12 patients).

The most important limitation of this preliminary data analysis is the short treatment time-period. As mentioned previously, it is not possible to draw long-term conclusions based on the current data. Also, due to the COVID-19 pandemic, enrolment was slowed (even halted), which resulted in a smaller study population than previously planned by the end of the first year of the study. This limits the strength of the statistical analysis, which affected the comparison of subgroups.

Real-World Evidence (RWE) studies are an important source of clinical information on the actual effectiveness of newly approved drugs, as they are conducted in a much less controlled environment, with the involvement of much more heterogenous patient populations compared to clinical studies [23]. As a recently approved drug there are only a few RWE studies on BDP/FOR/GB, but these reports similar clinical improvements in assessed parameters as the Randomized Clinical Trials (RCTs), however these studies only assessed severe and very severe COPD patients [24,25]. Even though the interim analysis of the Tri Optimize study has already presented promising results from moderate to severe COPD patient populations [26], the final subgroup analysis of this study is not yet available, making RATIONALE the first clinical study reporting on the efficacy of single inhaler triple combination only in moderate COPD patients, in a real-life setting. This population had not been selectively investigated by the aforementioned RCTs so there is very limited knowledge about the efficacy of triple therapy, especially on symptom severity. Another important strength of our study lies in the geographically diverse selection of outpatient care facilities all across Hungary, resulting in a representative study population. Finally, the possibility of accessing the database of the NHIF will provide a unique possibility to assess the adherence of patients to COPD medications in a real-life setting.

Comparing the efficacy of single inhaler triple therapy in patients with moderate *vs.* severe COPD could be an important possibility for future prospective trials, as it is the view of authors that early intensification of COPD therapy could be more beneficial for certain populations than a slow build-up.

Conclusion

We conducted a real-world non-interventional study and concluded that the administration of single inhaler triple combination therapy was beneficial for symptomatic patients with moderate COPD in the short term. Results of this analysis encourage the continuation of the study despite the difficulties of conducting studies in outpatient settings during the COVID-19 pandemic.

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Ethics Approval

All procedures were performed in accordance with the ethical standards of the National Scientific and Research Ethics Committee of Hungary (52301-1/2019/EKU) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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