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ORIGINAL RESEARCH

The Real-World Efficacy of Fixed Triple Inhalation Therapy in the Treatment of Moderate COPD Patients (RATIONALE Study)

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Purpose: COPD affects more than 300 million people worldwide, requiring inhalation treatment. Novel triple formulations of ICS, LABAs and LAMAs are becoming the mainstay of treatment, however there is still a lack of clinical evidence for personalized therapy.

Patients and Methods: RATIONALE was a non-interventional, prospective, 52 week study, assessing the effectiveness of beclometasone/formoterol/glycopyrronium-bromide (BDP/FF/G), in symptomatic COPD patients, with moderate airflow obstruction. The study included 4 visits, where data on demographic parameters, exacerbations, symptoms, quality of life (based on the EQ-5D-3L questionnaire) and lung function were collected. Data on adherence to treatment, based on prescriptions filled was collected from the database of the National Health Insurance Fund, with the patients' consent. The primary objective was the change of adherence to treatment during the study, compared to baseline.

Results: Altogether 613 patients had been enrolled. Their average age was 64.56 years and 50.5% were female. The average CAT score was 20.86, and most patients had suffered minimum one exacerbation (82.2%). Average FEV1 was 59.6%. Most patients had some limitation in one or more dimensions of EQ-5D-3L, with an average visual analogue scale score (VAS) of 60.31. After 12 months of treatment, adherence improved significantly – proportion of patients in the highest adherence group increased from 29.8% to 69.7% ($p<0.001$). The average CAT score improved by 7.02 points (95% CI 5.82–8.21, $p<0.001$). There was a significant improvement in all dimensions of EQ-5D-3L, with an average increase of 17.91 (95% CI 16.51–19.31, $p< 0.001$) points in the VAS score. Exacerbation frequency also decreased significantly.

Conclusion: Although limitations of observational studies are present, we observed that early introduction of fixed triple combination results in a marked improvement in adherence to treatment, symptom scores, exacerbation frequency and quality of life. The optimal choice of treatment is crucial for reaching the highest possible adherence.

Keywords: COPD, fixed triple combination, inhalation treatment, quality of life

Introduction

Chronic obstructive pulmonary disease (COPD) is the second most common respiratory disease and currently the third leading cause of death.[1] It affects over 300 million people worldwide, with 185,000 diagnosed patients in Hungary.[2] Its primary symptoms include exertional dyspnea, cough, and sputum production, significantly impacting patients' quality of life and daily activities. The disease progresses over time, leading to worsening respiratory function and exacerbation of symptoms despite appropriate treatment. Periodic acute exacerbations, triggered by viral or bacterial infections, air pollution, or other environmental factors, also characterize COPD.

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The goal of maintenance therapy for COPD is to reduce the risk of exacerbations, prevent their occurrence, alleviate daily symptoms, improve quality of life, and preserve respiratory function.[3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) provides guidelines for the diagnosis and management of COPD. The choice of maintenance therapy depends on exacerbation frequency and symptoms, particularly dyspnea.[4] Options include long-acting muscarinic antagonists (LAMA), beta-adrenergic agonists (LABA), dual bronchodilator therapy (LABA/LAMA), and combination therapy with inhaled corticosteroids (ICS/LABA). The latest treatment option includes fixed triple combination therapies containing three different active ingredients (ICS/LABA/LAMA), recommended when patients present with exacerbation and elevated blood eosinophil counts or when exacerbations occur despite established dual bronchodilator therapy.[4] The initiation of therapy with fixed triple combinations was newly introduced in the 2023 GOLD guidelines due to recognition of their high efficacy. Based on registry and real-world studies, fixed triple combination therapy has proven to be highly effective in high-risk patients, improving respiratory function, reducing exacerbation risk, alleviating symptoms, and potentially reducing mortality risk.[4]

Currently, three fixed triple combinations are available in Europe for COPD management, all approved by the European Medicines Agency (EMA): extrafine beclometasone/formoterol/glycopyrronium bromide (BDP/FF/G); fluticasone/vilanterol/umeclidinium (FF/VI/UMEC); budesonide/formoterol/glycopyrronium bromide (BUD/FOR/G).[5–7]

The efficacy of the BDP/FF/G combination was assessed in three separate studies comparing triple therapy to: a) LAMA (TRINITY) b) open triple combination (TRINITY); c) LAMA/LABA (TRIBUTE); d) ICS/LABA (TRILOGY).[8–10] The efficacy of FF/VI/UMEC and BUD/FOR/G fixed triple combinations was evaluated in two studies each, comparing them to ICS/LABA and LAMA/LABA therapies.[11–14]

All mentioned studies met their primary endpoints, demonstrating the efficacy of fixed triple combination therapies across various parameters. However, there are still patient groups where evidence of the benefits of triple therapy is lacking, such as comparisons with free triple therapies in real-world settings. Adherence to multi-inhaler triple therapy in routine clinical practice is known to be poorer than with fixed combinations, potentially influencing therapeutic outcomes.[15] Additionally, the efficacy of triple combination therapy in patients with moderate COPD (50<FEV1<80%) remains uncertain, as some studies excluded these patients entirely while others included them in low proportions.[9–14]

Patients with mild or moderate COPD can still experience severe symptoms, as FEV1 poorly correlates with symptom severity. Therefore, the 2017 GOLD guidelines state that FEV1 values do not influence therapeutic classification or treatment selection. However, it's well-established that even in mild and moderate airway obstruction, there are structural changes in the lungs and inflammation in the small airways, which are also poorly predicted by FEV1. Some authors have suggested earlier therapeutic interventions in mild and moderate COPD due to the significance of small airway disease (SAD).[16]

Our study, RATIONALE, uniquely focused on patients with moderate airflow obstruction (50% <FEV1 < 80%). In this four-visit study with a 52-week follow-up, clinically relevant and statistically significant improvements in all endpoints (CAT, SpO1, EQ-5D-3L quality of life questionnaires, cough-sputum) were observed after just one month. Data from the first two visits were presented as an interim analysis.[17] In this article, we present the full analysis following study completion.

Material and Methods

RATIONALE was a non-interventional, multicentre, prospective study to assess the efficacy of extrafine BDP/FF/G in everyday clinical practice after its use was initiated by a pulmonology specialist. Switching to BDP/FF/G was based on the physicians' decision and preceded the patients' enrollment in the study. BDP/FF/G was prescribed according to its Summary of Product Characteristics and to the Hungarian national protocols of COPD maintenance therapy. All off-label usages were recorded and reported to the authorities. The study was approved by the National Institute of Pharmacy and Nutrition (approval No.: OGYÉI/71963-5/2019) based on the beneficial assessment of the National Scientific and Research Ethics Committee of Hungary and was conducted according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

Further details of the study were previously reported in the pre-planned interim analysis.[17]

Patients and Procedures

Eligibility criteria for patient inclusion were the following: specialist diagnosed COPD patients, ≥35 years of age; considered high risk for exacerbations (had suffered one or more severe or two or more moderate exacerbations in 12 months prior to study inclusion) or had had their maintenance treatment switched before, due to being high risk for exacerbations; symptomatic patients (COPD Assessment Test - CAT≥10 and/or modified Medical Research Council score - mMRC≥2); having moderate airflow limitation (80%> FEV1≥ 50%); finally, patients switched from fixed dual combinations (ICS and LABA or LABA and LAMA in single inhaler) or from open triple combination to fixed BDP/FF/G were eligible for inclusion. COPD patients are only diagnosed and managed by pulmonologist specialists in Hungary, meaning a much lower chance of misdiagnosis compared to countries where non-specialists can also treat these populations. Due to the non-interventional nature of the study further diagnostic measures were not expected of the enrolling investigators. All inclusion criteria were listed in the previously published interim analysis. Eligible patients were followed for 12 months. Baseline data were collected upon enrollment (visit 1- V1), and they included age, sex, demographic data, physiological parameters (heart rate, blood pressure, oxygen saturation), lung function, COPD specific assessment (CAT, mMRC, number of exacerbations), previous and new maintenance therapy, frequency and subjective severity of cough and sputum production, data on inhalation technique assessment and quality of life, according to the EQ-5D-3L questionnaire. Follow-up visits were conducted 1 month (V2), 6 months (V3) and 12 months (V4) after V1. Data on COPD specific assessment, cough and sputum production, EQ-5D-3L and inhalation technique assessment were collected at each visit, while data on comorbidities were collected only at V4. All safety data were collected at each visit.

Besides providing informed consent for study inclusion, patients also agreed to the handling of their social security number by the Primary Investigator for the reason of obtaining further data from the National Health Insurance Fund (NHIF). The NHIF collects all data on reimbursed healthcare resource use (in- and outpatient procedures, drug prescription, laboratory tests and imaging etc). These data can be accessed in aggregated form for research purposes on a claim basis. Due to personal information handling laws, it is not possible to obtain any data of groups having less than 10 patients. In this study we aimed to collect data on medication prescriptions filled to assess adherence during the study and one year prior to inclusion.

Data on medication prescriptions was collected from the NHIF database, where the act of filling a prescription is also recorded. We assumed that filling of a prescription was equal to the actual use of the medication. Adherence was calculated by dividing the days covered by treatment, based on the days of therapy (DOT) value of each medication, by the overall follow-up time.

Data on exacerbations were collected and analyzed in two ways. All data on exacerbations were collected by physicians, upon each visit. Moderate exacerbations were classified as an acute worsening of COPD symptoms requiring the use of oral corticosteroids and/or antibiotics, while severe exacerbations were defined as acute worsening of COPD symptoms requiring hospital or emergency ward admission. Also, data from the NHIF database was collected on exacerbations, where moderate exacerbation was defined as a prescription for oral corticosteroid and/or antibiotics with the International Classification of Diseases (ICD-10) code of COPD (J44). While severe exacerbations were defined as hospital or emergency ward admissions with the ICD-10 code of COPD (J44). Similar definitions had been used in retrospective financial database analyses before,[18–20] but their sensitivity had never been tested against real-life data. Our aim was also to assess differences in the two definitions for exacerbations.

Outcomes

The primary objective of the RATIONALE study was to assess the change in adherence to treatment between the study time and the previous year, based on the prescription data received from the NHIF.[18–20]

Secondary endpoints included change from baseline in CAT, domains of the EQ-5D-3L, severity and frequency of cough and sputum production, exacerbation rates and physiological parameters after 12 months of treatment with BDP/FF/G. All parameters were also assessed at each visit (V2 and 3), except for exacerbation rates.

Statistical Analysis

After data collection and cleaning, the collection of social security numbers (SSN) was performed by the PI of the study. Unfortunately, due to the COVID-19 pandemic, the study conduction was prolonged, and many investigators had been reassigned to other geographical area as part of the pandemic mitigation strategy of the Hungarian government. Due to these factors, unfortunately many patients' SSN was impossible to collect. This resulted in the exclusion of these patients from the study's final analysis.

For the comparison of baseline parameters, we used descriptive statistics. For comparison of results between the first and last visits, mixed linear models were used for numerical outcomes and mixed binomial regression models for dichotomous variables. Odds ratios (ORs) were provided with 95% confidence intervals (95% CI). The regression model included the following explanatory variables: visit, gender, age group, number of exacerbations (0, 1, 2, >2) and pack/year as fix factors, and the patient ID as a random factor. We did not suppose any interaction. The age groups were 0–49, 50–59, 60–69, 70–79 and 80-. We considered 0 packs/year for nonsmokers.

We also planned to use the smoking status, which is hardly associated with pack/year. The models did not converge if smoking status was also included. Some categorical variables had more than two levels, eg, severe, moderate, and no pain. In those cases, two binomial models were used. The first considered the frequency of the severe pain, and the second considered the frequency of the severe and the moderate pain as a composite event.

Results

The study was conducted between February 18th, 2020, and January 31st, 2023. A total of 1148 patients were screened, and 1046 patients were enrolled in the study. 924 patients completed the study. 15 patients died during follow-up, none were associated with the investigated medications. One patient withdrew consent from participation, 9 patients had protocol violations (visit date was out of the prespecified schedule), and 97 patients were lost to follow-up. Unfortunately, the social security numbers of only 648 patients were available for collection, and in 35 cases, an invalid SSN was provided, resulting in the final study population of 613.

The enrolled patients comprised 50.5% females (310 individuals). The mean age of the patients was 64.56 years (95% CI 63.82–65.03). Among them, 332 patients (55.2%) were active smokers, while 74 patients (12.1%) were non-smokers. The average BMI was 28.83 (95% CI 28.28–29.39), indicating that the majority of enrolled patients were overweight.

Regarding previous therapy, 289 patients (47.2%) were on LABA/LAMA therapy, 168 patients (27.4%) were on open triple therapy, and 156 patients (25.5%) were on ICS-LABA combination therapy. The mean CAT score at baseline was 20.86 (95% CI 20.24–21.48), with 68% of patients experiencing at least two moderate exacerbations in the previous 12 months, and only 17.8% not experiencing any exacerbations. According to the EQ-5D-3L questionnaire, most patients had some degree of limitation in all five domains. The mean Visual analogue scale (VAS) score at baseline was 60.31 (95% CI 59.11–61.52) on a scale of 0–100. The average FEV1% predicted value was 59.6% (95% CI 59.01–60.19%).

Only three cases of adverse drug reactions were reported all of which were within the already known to be associated with the investigated drug. These patients treatment had been switched to their earlier maintenance therapy and were excluded from analysis.

Similar results were observed among patients receiving open triple therapy, before enrollment. Detailed descriptive data are presented in Table 1.

Adherence

We calculated PDC (Proportion of Days Covered) in the 365 days before and after the inclusion. A day was covered before the inclusion if the patient had all necessary active substances on that day, and after the inclusion if they had the BDP/FF/G. Significant improvement in adherence was observed based on prescriptions data of purchased drugs in pharmacies. While only 29.4% of patients belonged to the 80–100% adherence group at baseline, at the end of the study, 69.7% of patients were in this group, indicating much better adherence after switching to fixed triple therapy. Compared to 27.6% at baseline, only 3.4% of patients belonged to the least adherent (0–19% coverage) group by the end of the study.

Table 1 Baseline Characteristics of Enrolled Patients

		All Patients (N=613)	Switched from Open Triple (N=168)	Switched from Dual Therapy (N=445)
Sex	**Male**	49.4%	47.6%	50.1%
	Female	50.6%	52.4%	49.9%
Age		64.56 (9.28)	65.39 (9.53)	64.25 (9.18)
Body Mass Index		28.83 (6.95)	28.7 (6.12)	28.89 (7.25)
Smoking habits	**Smoker**	54.2%	51.2%	55.3%
	Ex-smoker	33.8%	35.7%	33.0%
	Nonsmoker	12.1%	13.1%	11.7%
Highest level of education	**Primary school**	41.4%	38.1%	42.7%
	Secondary school	53.8%	56.5%	52.8%
	University	4.7%	5.4%	4.5%
	No data	0.3%	1.2%	0.5%
Occupation	**Blue collar**	26.8%	24.4%	27.6%
	White collar	7.7%	7.1%	7.9%
	Retired	57.3%	61.3%	55.7%
	Retired with disability	8.3%	7.1%	8.8%
COPD Assessment Test score		20.86 (7.81)	20.85 (7.35)	20.86 (7.98)
Number of exacerbations	**0**	17.8%	17.3%	18.0%
	1	14.2%	11.9%	15.1%
	2	62.2%	66.1%	60.7%
	2<	5.9%	4.8%	6.3%
Average FEV1		59.6 (7.47)	58.69 (6.94)	59.95 (7.64)
Coughing as a symptom present		95.4%	93.5%	96.2%
Sputum as a symptom present		84.3%	81.6%	85.4%
HRQoL VAS score (0–100)		60.31 (15.25)	59.49 (15.26)	60.63 (15.25)
Adherence	**0–19%**	27.6%	18.5%	31.0%
	20–39%	9.3%	6.0%	10.6%
	40–59%	15.8%	16.7%	15.5%
	60–79%	17.9%	21.4%	16.6%
	80%=<	29.4%	37.5%	26.3%

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; FEV1, Forced Expiratory Volume in 1 second; HRQoL, Health Related Quality of Life; VAS, Visual Analogue Scale.

Similar results were seen in the group of patients switched from triple therapy. Here, the proportion of patients with adequate adherence increased from 37.5% to 72% ($p<0.001$), while the proportion of patients with the worst adherence decreased from 18.5% to 4.2%. The results of the primary endpoint are presented in Figure 1.

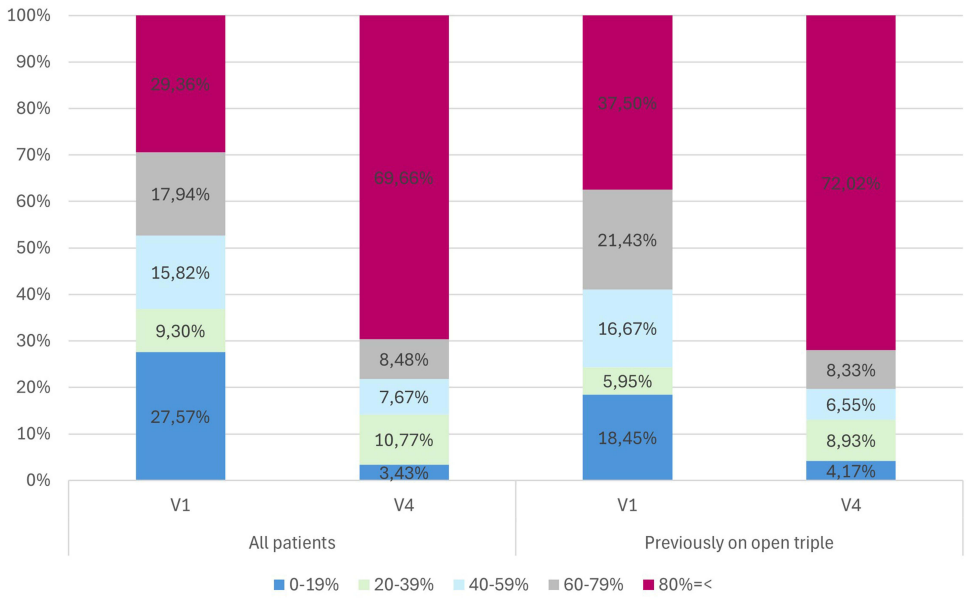

Figure 1 Changes in adherence to inhalation treatment according to medication prescriptions filled before study inclusion and at study end.

Symptoms

There was statistically significant and clinically relevant improvement in all parameters assessed.

According to the CAT questionnaire, there was an average improvement of 7.02 points (95% CI 5.82–8.21, p<0.001). The improvement in CAT score far exceeded the minimal clinically important difference (MCID) of >2 points within 2–3 months.

Currently, there is no universally accepted clinical measure of the degree of cough and sputum production, so in our study, we assessed the occurrence of these symptoms in the week before the visit. These parameters reflect the subjective opinion of the enrolled patients, so no minimal clinically relevant change can be provided. At the start of the study, more than 95.4% of patients complained of cough, and 84.3% of sputum production, after the introduction of triple therapy, these values decreased to 56.9% and 42.7%, respectively (p<0.001 in both cases).

Based on the four-point mMRC, at baseline, the vast majority of patients were in the 2 (66.7%) and 3 (31.5%) mMRC categories. This distribution significantly changed by the fourth visit, where 92.6% of patients were in the 2 and 5.1% in the 3 mMRC categories. These changes were statistically significant in intergroup comparisons (p<0.001).

Similar improvements were observed in all the above parameters among patients switched from triple therapy. The CAT score decreased by an average of 7.02 points (95% CI 5.82–8.21, p<0.001), which also significantly exceeded the MCID. The extent of improvement in CAT scores is shown in Figure 2. The proportion of patients complaining of cough decreased from 93.5% to 55.7%, while the proportion of patients complaining of sputum production decreased from 81.6% to 43.1% (p<0.001 for both). The distribution of patients by mMRC scores showed a similar pattern in the group of patients switched from triple therapy (67.3% in the mMRC 2 category, 31.3% in the mMRC 3 category). A similar change was observed in the entire patient group, with 87.8% of patients in the mMRC 2 category and 8.8% in the mMRC 3 category by the end of the study (p<0.001).

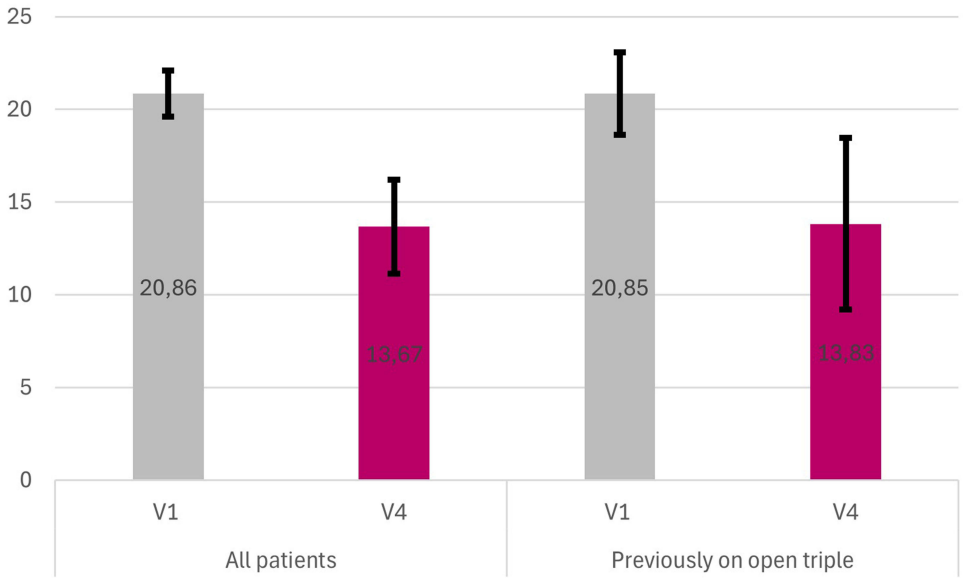

Figure 2 Changes in CAT scores from baseline to V4 in all patients and patients switched from open triple combinations.

Quality of Life

The EQ-5D-3L questionnaire assesses five dimensions of life quality (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at three levels (no problems, some problems, and extreme problems). Additionally, during questionnaire completion, patients must evaluate their subjective life quality on a 0–100 VAS.

At baseline, 34.4% of patients reported some difficulty with walking, which decreased to 19.9% by the end of the study, while the proportion of patients who had no problem with walking increased from 65.6% to 80% ($p < 0.001$). There was no patient at any visit of the study who reported severe problems in this dimension. At the start of the study, a total of 2 patients (0.3%) indicated being unable to perform self-care or dress themselves, and by Visit 4, no patient remained in this group. At enrollment, 27.1% had moderate limitations, which decreased to 7.4% by the end of the study. The proportion of patients without problems increased to 92.7% by the end of the study. Regarding usual activities, at enrollment, 4 patients reported severe limitations (0.7%), while 57.4% had moderate limitations, and less than half (41.9%) reported no problems in performing daily activities. By the end of the study, the proportions changed to 0.2% severe, 26.4% moderate limitations, and 73.5% without limitations. At baseline, 2.9% of patients reported severe pain, 59.4% moderate pain, and only 37.7% reported no pain/discomfort. These proportions changed to 0.5% severe, 28.8% moderate, and 72.7% no pain/discomfort by Visit 4. At baseline, more than half of the patients reported any type of anxiety or depression, with 6.5% reporting severe symptoms, 48.5% moderate, and only 45% reporting no anxiety or depression. By the end of the study, these proportions changed to 0.7% severe, 22.8% moderate, and 76.6% no anxiety or depression.

For all the above improvements, the increase in the proportion of patients without problems was statistically significant ($p < 0.001$ in all cases). The improvement rates are shown in Figure 3. On average life quality measured by VAS increased by 17.91 points from V1 to V4 (95% CI 16.51–19.31, $p< 0.001$) due to the fix triplet therapy, which far exceeded the MCID[21] of 8 points for VAS. Similar improvements were observed in all dimensions and in VAS values for patients switched from open triple to fix triple therapy. Detailed results are presented in Table 2.

Exacerbations

In the 12 months preceding enrollment, 14.2% of patients experienced one moderate-to-severe exacerbation, 62.2% experienced two, and 5.9% experienced more than two exacerbations. Only 17.8% of patients did not experience any exacerbations during the preceding 12 months. By the end of the study, the proportion of patients experiencing exacerbations significantly decreased, with 14.7% experiencing one, 14.4% experiencing two, and only 0.7% experiencing more than two moderate-to-severe exacerbations. Accordingly, the proportion of patients who did not experience exacerbations increased to 70.2% ($p < 0.001$ for comparisons between individual groups).

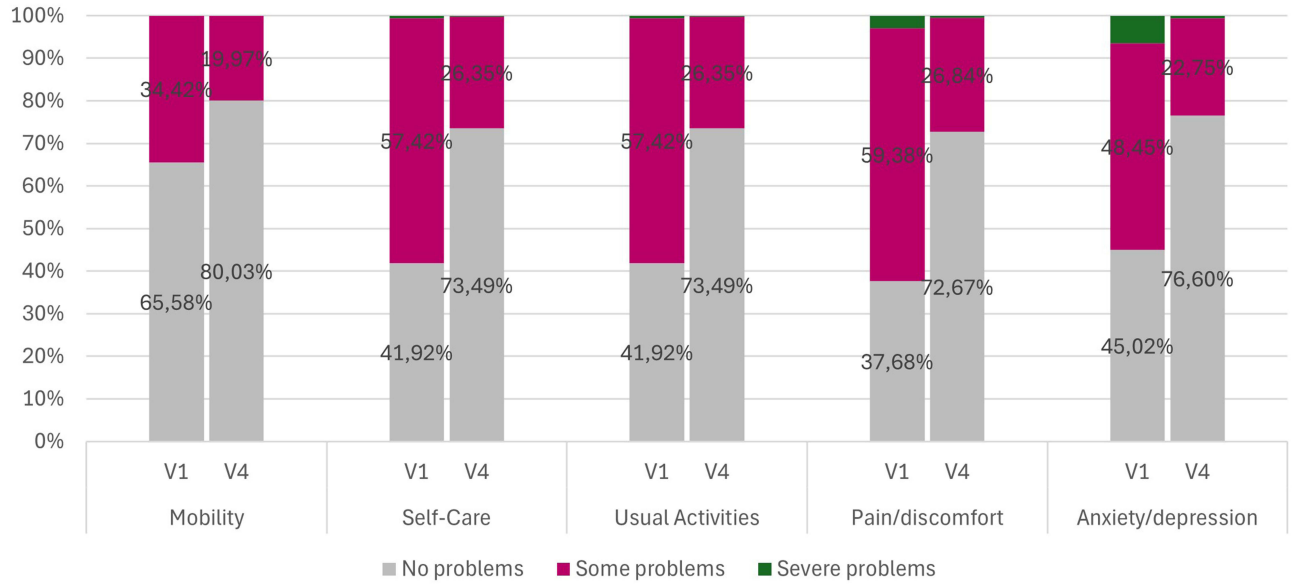

Figure 3 Change in E5-5D-3L domains between baseline (V1) and Visit 4 (V4).

Similar results were observed at enrollment (see Table 1) and at the end of the study among patients switched from open triple therapy. The proportion of patients experiencing two or more exacerbations significantly decreased (from 66.2% to 12%, and from 4.8% to 0.6%, respectively). Meanwhile, the proportion of patients experiencing exactly one exacerbation increased slightly (from 11.9% to 13.70%), and the proportion of patients not experiencing exacerbations increased significantly, from 17.3% to 73.7%. The improvement in exacerbation outcomes is illustrated in Figure 4.

When exacerbation frequency was assessed based on NHIF data, similar changes were observed, albeit in smaller numbers.

Table 2 Proportion of Patients in the EQ-5D-3L Groups Among Patients Previously on Open Triple Combinations

		V1	V2	V3	V4
Mobility	Some problems	35.1%	24.4%	22.2%	21.6%
	No problems	64.9%	75.6%	77.8%	78.4%
Self-Care	Some problems	29.2%	16.7%	11.4%	10.2%
	No problems	70.8%	83.3%	88.6%	89.8%
Usual Activities	Severe problems	1.2%	0.0%	0.0%	0.6%
	Some problems	57.1%	36.9%	35.9%	34.7%
	No problems	41.7%	63.1%	64.1%	64.7%
Pain/discomfort	Severe problems	1.8%	0.6%	0.0%	1.2%
	Some problems	63.7%	40.5%	32.3%	28.1%
	No problems	34.5%	58.9%	67.7%	70.7%
Anxiety/depression	Severe problems	6.0%	2.4%	1.8%	1.2%
	Some problems	45.8%	35.1%	27.5%	24.0%
	No problems	48.2%	62.5%	70.7%	74.9%

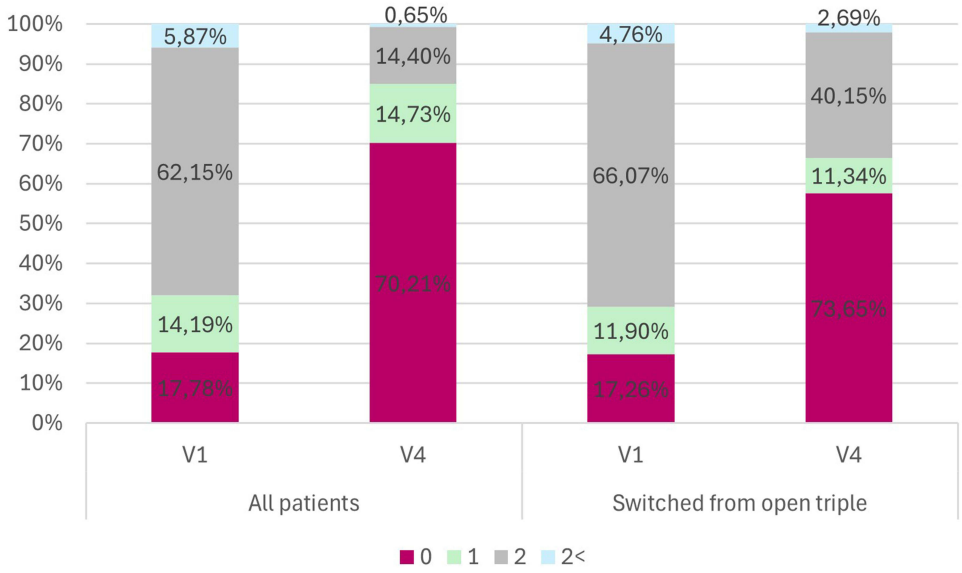

Figure 4 Change in exacerbation frequency between baseline (V1) and Visit 4 (V4).

Discussion

The uniqueness of the RATIONALE study lies in the exclusive inclusion of frequent exacerbator COPD patients with moderate airflow obstruction (50% <FEV1 <80%). In this four-visit, 52-week follow-up study, clinically and statistically significant improvements were observed in all endpoints (CAT, SpO2, EQ-5D-3L quality of life questionnaires, cough-sputum production) after just one month,[17] and these significant improvements were sustained for the measured parameters at the end of the study. It is important to highlight that unlike registration trials, where patients were previously on LABA/LAMA or ICS/LABA therapy, 28% of patients were switched from free triple combination therapy. For each patient group, switching to the extrafine BDP/FF/G fixed combination resulted in significant improvements in symptoms, quality of life, and exacerbation frequency.

The efficacy of BDP/FF/G has been thoroughly investigated in large randomized clinical trials in the late 2010s for drug registration purposes. However, real-world studies are needed to further confirm its effectiveness, broaden its applicability, supplement trial data, and expand healthcare professionals' practical experience. Patients were enrolled in the RATIONALE study according to the BDP/FF/G prescribing information and national financing protocol, reflecting real-world clinical practice. Remarkably positive outcomes were achieved in this real-world patient group following therapy switch.

The main endpoint of the study was the improvement in therapeutic adherence. Significant and substantial improvement in adherence was observed with the extrafine fixed triple combination. One reason for this could be the effectiveness of the therapy, leading to increased adherence due to reduced symptoms. It is important to note that adherence assessment was based on data from the financing database, rather than patient self-report, making it a more objective measure. However, it should be noted that medication dispensation does not equate to actual usage. Another important limitation is the possibility of a "study effect", where patient participation in the study itself motivates more adherent medication use. Nonetheless, the substantial increase in adherence (137% increase in adherence rate) over a long period (12 months) and the method of assessment independent of self-reporting suggest greater adherence resulting from effective medication management. It is also important to highlight that a similar radical improvement was seen in patients who received open triple combinations prior to inclusion.

The RATIONALE study demonstrated significant improvement in health status due to extrafine BDP/FF/G therapy in terms of symptomatic control. This improvement is objectively reflected in the decrease in CAT and mMRC questionnaire scores. The average improvement in CAT score was 7.02 points, exceeding the minimally clinically relevant change for CAT.[22] Since there is currently no universally accepted method for assessing cough and sputum production,

we focused on the frequency of these symptoms, which also showed significant improvement. Despite being considered inherent to COPD, this study highlights that the realistic goal of modern inhalation therapy is achieving complete symptom relief or at least minimizing symptoms.

In addition to symptoms, we assessed the quality of life of enrolled patients using the validated EQ-5D-3L questionnaire, which examines five domains: mobility, self-care, usual activities, pain, anxiety, and depression, along with a VAS score at each visit. It is noteworthy that despite enrolling patients with moderate airflow obstruction, traditionally considered as milder COPD, they reported particularly poor baseline quality of life scores in both individual domains and VAS scale values. Significant improvements were reported in all five domains for patients switched to triple therapy, indicating a substantial overall improvement in factors that previously significantly limited their quality of life.

Among the five domains, the most significant reduction was observed in anxiety, as international data indicate that anxiety affects 7–50%[23] of COPD patients, while local, Hungarian results showed its presence in 22%[19] of patients who suffered an exacerbation. In addition to its frequency, anxiety is highly important as its presence negatively affects patients' symptomatic control.[24] Reduction in anxiety due to therapy is therefore crucial for improving quality of life and symptom severity.

Regarding the VAS scale used to assess quality of life, there was an average improvement of 17 points compared to the baseline score, far exceeding the minimal clinically relevant increase of 8 points. This improvement highlights that while COPD is a lifelong, progressive disease, monitoring patients' quality of life is a crucial task, as improving it is an achievable therapeutic goal.

Preventing exacerbations is the most important task in COPD management, as these events significantly increase patients' symptoms, worsen their lung function, reduce their quality of life, and increase their mortality risk. One of the most important outcomes of fixed triple combinations was the additional reduction in exacerbation risk compared to all available therapies so far. This result gains further confirmation in real-world studies - in the TRICOP[25] study investigating the real-world effectiveness of BDP/FF/G, exacerbation rates decreased by 57% for moderate and 27% for severe exacerbations, while according to another survey, the Italian TRITRIAL[26] study, the proportion of patients experiencing moderate exacerbations decreased from 89.0% to 14.6%, and severe exacerbations decreased from 27% to 5.4%. Similar positive results were achieved in our study, further enhancing the evidence supporting the effectiveness of fixed triple combinations.

In randomized controlled clinical trials, there was no significant difference in COPD exacerbation occurrence, lung function change, and quality of life between free triple combination and single inhaler triple therapy.[27] However, real-world data indicate higher patient adherence with single inhaler triple therapy compared to free combinations.[28] More than half of the patients enrolled in the TRICOP study received free triple combination therapy before enrollment. Patients switched to single inhaler fixed triple therapy achieved better results in terms of symptomatic control and quality of life improvement compared to those on free triple combination therapy.[24] Similarly, patients enrolled in the TRIOPTIMIZE[29] study, where nearly 60% received free triple combination therapy before inclusion, showed less improvement in symptomatic control and quality of life with single inhaler fixed triple therapy compared to the groups who had received other maintenance therapies before inclusion. However, in our own study, similar efficacy was observed in patients switching from free triple combination and dual therapies.

Among the strengths of the study, it is noteworthy that data collection occurred under monitored conditions, and the study was the first to directly examine the effectiveness of ICS/LABA/LAMA combination therapy in patients with moderate airflow obstruction due to COPD. In line with GOLD recommendations, it can be concluded that the effectiveness demonstrated in RCTs is also present in the moderate group, beyond the severely obstructed patient population, hence exacerbation rate and symptom severity should be considered in choosing maintenance therapy.

One limitation of the study is the absence of a comparative or control arm, which limits the interpretation of results to changes relative to the baseline. Additionally, a limitation but also a strength was that patients used various medications before their inclusion. An important limitation of the study lies in it's observational nature, where confounding effects of the environment cannot be excluded. Another limitation lies in the measurement of adherence, where we had to work on the assumption that filling a prescription is equal to using it. However, it is also important to highlight, that measuring adherence this way is still much more reliable than basing adherence of patients' report. Finally, the social distancing and

lockdowns could have a decreasing effect on exacerbation rates, which could affect our outcome. However, more than half of the study participants were enrolled in 2021-'22, meaning that their baseline year was also during the pandemic, reducing this effect.

Overall, we can state that after changing the treatment to extrafine single inhaler triple therapy a clinically and statistically significant improvement was observed in adherence to treatment, symptoms scores, and exacerbation rates as well, in a COPD population with moderate airflow limitation. These result are encouraging for initiating triple therapy earlier, which is in line with new international recommendations. Also, a huge improvement in adherence was observed which might be due to the improvement in symptoms, which reinforces adherent use of medications. Further studies are needed to assess if this improvement in adherence endures long-term as well. Due to the study's observational nature, many environmental factors (such as, the study effect, and the effect of the COVID-19 pandemic) cannot be excluded, so further studies are warranted to reinforce these findings.

Conclusion

In line with previous studies, we can conclude that the early introduction of the extrafine ICS/LABA/LAMA combination significantly and clinically relevantly improves patients' quality of life, symptoms, and exacerbation risk.[8–10]

Overall, we can ascertain that ICS/LABA/LAMA combination therapy can be effectively applied not only in the group of COPD patients with severe airflow obstruction, but also significant symptomatic improvement and quality of life benefits can be achieved in the moderate COPD, frequently exacerbating group as well. Our study also showed that a similar improvement could be achieved after switching from open to fix triple therapy.

Additionally, our study indicates that patients' adherence is quite low in real-life settings, while the results proved that improving adherence significantly enhances therapeutic outcomes. Therefore, in addition to selecting the right therapy for COPD patients, improving patient cooperation and increasing drug use to an optimal level are crucial tasks for healthcare providers in the case of non-adherent patients to improve clinical outcomes.

Ethics Approval and Informed Consent

The study was approved by the National Institute of Pharmacy and Nutrition (approval No.: OGYÉI/71963-5/2019) based on the beneficial assessment of the National Scientific and Research Ethics Committee of Hungary and was conducted according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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