Impact of elexacaftor/tezacaftor/ivacaftor combination therapy on body plethysmography in adults with cystic fibrosis: Beyond FEV_1

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ABSTRACT

INTRODUCTION The treatment approach involving a combination of three cystic fibrosis (CF) transmembrane conductance regulatory (CFTR) protein modulators (elexacaftor, tezacaftor, ivacaftor) in the treatment of CF patients has provided beneficial results on FEV_1.

METHODS The aim of the retrospective single-center observational study was to show the impact of elexacaftor/tezacaftor/ivacaftor with special emphasis on full body plethysmography, exercise capacity and quality of life. Adult cystic fibrosis patients were evaluated after the initiation of triple CFTR therapy between July 2020 and March 2021. A two-tailed t-test for dependent samples with Bonferroni correction was used to compare outcomes between the two visits.

RESULTS A total of 38 adult CF-patients (20 females), aged 37.2 ± 11.6 years were included in the study. The analysis shows significant improvements in FEV_1 and vital capacity (VC). The Tiffeneau-Index (FEV_1/VC) only showed a minor increase from 59 ± 14% to 62 ± 13%. Hyperinflation (RV) and effective specific airway resistance (sRAWeff) significantly improved such as exercise capacity (6MWD) and CFQ-R. sRAWeff showed a strong significant association with an improvement in exercise capacity (Pearson's r=0.593; 95% CI: 0.296–0.786, p<0.001) and FEV_1 (Pearson's r=0.560; 95% CI: 0.292–0.746, p<0.001) while all other parameters did not show significant correlations.

CONCLUSIONS Triple CFTR modulator therapy improves not only FEV_1 but also airway resistance and pulmonary hyperinflation. This is most reliably assessed by measuring sRAWeff, which is associated with exercise capacity, representing the work of breathing. Futures studies should incorporate body plethysmography assessments especially in patients with limited ability to perform spirometry or with non-reproducible spirometry results.

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KEYWORDS

cystic fibrosis, body plethysmography, spirometry, pulmonary function testing, FEV_1, CFTR modulator triple therapy, elexacaftor, tezacaftor, ivacaftor

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INTRODUCTION

Cystic fibrosis (CF) is a genetic disease caused by dysfunction of the CF transmembrane conductance regulatory (CFTR) protein, which results in the accumulation of viscous mucus in several organs[1,2]. The respiratory system is particularly affected and often impacted by mucus, whereby the ensuing complications can lead to reductions in both life expectancy and health-related quality of life (HRQL)[2]. The treatment approach involving a combination of three CFTR modulators (elexacaftor, tezacaftor, ivacaftor) is causal, easy to administer and has shown very promising results. Most importantly, this treatment approach has been shown to significantly improve lung function, as evidenced by an improvement in forced expiratory volume in one second (FEV_1)[3,4].

Nonetheless, the impact of this combination regimen on respiratory physiology needs to be investigated further, since lung function has so far mostly been evaluated by spirometry. For this reason, the present study investigated adult cystic fibrosis patients after (follow-up) the initiation of triple therapy with elexacaftor/tezacaftor/ivacaftor. Spirometry, full body plethysmography, and the assessment of the diffusion capacity were performed in all subjects, in line with previously established recommendations[5-7].

METHODS

This retrospective single center study investigated adult cystic fibrosis patients after the initiation of triple CFTR

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therapy between July 2020 and March 2021 to explore the change of body plethysmography parameters together with measurements of exercise capacity and quality of life.

The two-tailed t-test for dependent samples with Bonferroni correction was used to compare outcomes between the two visits. Primary endpoint was the change in effective specific airway resistance (sRAWeff). Additional spirometry and body plethysmography parameters, 6-minute walking test and the Cystic Fibrosis Questionnaire–Revised (CFQ-R) served as secondary outcomes. Pearson's correlation coefficient (r) was calculated for changes in sRAWeff, residual volume (RV), FEV1, the CFQ-R respiratory domain, and the 6-minute walking distance (6MWD).

RESULTS

A total of 38 patients were included: 20 females (52.6%); mean age 37.2 ± 11.6 years; body mass index 21.6 ± 5.1 kg/m^2; FEV_1 60.2 ± 20.3; intrathoracic gas volume (ITGV) 147 ± 33; residual volume (RV) 169.9 ± 59.9; total lung capacity (TLC) 112.8 ± 20.4 and sRAWeff: 282 ± 161, each percent predicted; 6MWD 583.1 ± 90.8 m; and CFQ-R respiratory domain 62.6 ± 18.3 points. Phe508del mutations were homozygous in 50% (n=19). The mean time between the compared visits was 16 ± 4 weeks, the mean time between the first visit and therapy initiation was 4 ± 3 weeks. In one patient, the first visit was seven days after the first dose of triple therapy. Time to the follow-up visits after triple

Table 1. Changes in spirometry, body plethysmography, 6-minute walking distance and health-related quality of life following elexacaftor/tezacaftor/ivacaftor combination therapy in adult cystic fibrosis patients (N=38)

	Mean difference (99.55% CI)	p*	n
Spirometry parameters			
VC (%predicted)	9.6 (4.9–14.3)	<0.0000	37
FEV_1 (%predicted)	10.7 (6.7–14.7)	<0.0000	37
PEF (%predicted)	13.7 (7.7–19.6)	<0.0000	37
Body plethysmography parameters			
Resistance			
RAWeff (%predicted)	-31.3 (-73.6–11.0)	0.0332	36
sRAWeff (%predicted)	-65.1 (-111.1 – -19.1)	<0.0000	37
Lung volume			
ITGV (%predicted)	-13.2 (-28.8–2.4)	0.0158	36
RV (%predicted)	-34.5 (-66.8 – -2.2)	0.0029	36
TLC (%predicted)	-4.8 (-13.3–3.7)	0.1031	37
Diffusion capacity			
TLCO (%predicted)	3.1 (-0.8–6.9)	0.0232	35
KCO (%predicted)	-4.1 (-8.1 – -0.0)	0.0048	35
6-minute walking test			
6MWD (m)	45.2 (10.9–79.6)	<0.0004	29
Health-related quality of life	**Points (98.75% CI)**	**p§**	**n**
CFQ-R			
Respiratory domain	23.1 (13.9–32.4)	<0.0000	29
Physical domain	14.7 (6.6–22.4)	<0.0000	30
Vitality domain	19.4 (10.4–28.3)	<0.0000	30
Treatment burden domain	5.0 (-1.8–11.8)	0.0601	30

ITGV: intrathoracic gas volume. VC: volume capacity. FEV_1: forced expiratory volume within the first second. PEF: peak expiratory flow. RAWeff: effective airway resistance. sRAWeff: effective specific airway resistance. RV: residual volume. TLC: total lung capacity. TLCO: diffusion capacity. KCO: Krogh factor (TLCO/VA). 6MWD: 6-minute walking distance. CFQ-R: Cystic Fibrosis Questionnaire – Revised: Scores on the CFQ-R range from 0 to 100, with higher scores indicating a higher participant-reported quality of life (minimal clinically important difference for the respiratory domain: 4 points). *P-value and confidence interval (CI) for two-tailed t-test for dependent variables: p<0.0045, indicating statistical significance according to Bonferroni correction. § P-value and confidence interval (CI) for dependent variables: p<0.0125 indicating statistical significance according to Bonferroni correction.

therapy initiation was 13 ± 2 weeks.

The main results are summarized in Table 1 and are as follows: The analysis shows significant improvements in FEV_1 and vital capacity (VC). Therefore, the Tiffeneau-Index (FEV_1/VC) only showed a minor increase from 59 ± 14% to 62 ± 13%. Hyperinflation (RV) and the primary outcome (sRAWeff) significantly improved such as exercise capacity and CFQ-R. sRAWeff showed a strong significant association with an improvement in exercise capacity (6MWD) (Pearson's r=0.593; 95% CI: 0.296–0.786, p<0.001) and FEV_1 (Pearson's r=0.560; 95% CI: 0.292–0.746, p<0.001) while all other parameters did not show significant correlations.

DISCUSSION

The additional assessment of sRAWeff in CF treatment offers three potential advantages: Firstly, sRAWeff measurements occur during quiet breathing, are directly assessed by breathing loops and therefore independent from the forced respiratory maneuvers. This has proven to be advantageous in children and other patients with limited ability to perform spirometry or with non-reproducible spirometry results. Secondly, sRAWeff measurements address the interplay of airway obstruction and lung volume[7]. Thus, sRAWeff is suggested to represent a flow-standardized, volume-related work of breathing[7]. It is therefore conceivable that changes in sRAWeff are closely related to exercise capacity, as assessed by the 6MWD and as suggested by the present data.

Based on these findings, CFTR modulator treatment has the potential to improve both airway obstruction and hyperinflation, and these intricate lung function improvements are not fully detectable by spirometric measurements alone. However, in view of the current finding, improvements in FEV_1 are suggested to reflect two different changes in respiratory mechanics: 1) an improvement in airway obstruction, 2) a recruitment in lung volumes as a consequence of an improved VC at a cost of a reduced RV (mucus clearance).

These observations also confirm previous radiological findings that showed areas with reduced mucus impaction following treatment and significantly augment research that identified the peripheral lung as an important site of therapy effect[8,9].

Therefore, thirdly, the assessment of sRAWeff and RV is another method to easily determine if mucus is impacting the respiratory tract. Since the aim of CFTR modulation is to liquefy mucus and to reduce its amount, the success of CFTR modulation therapy might be enhanced when treatment is supplemented with intensified airway clearance techniques, which should be investigated in future studies.

Limitations

This study has limitations, due to its retrospective design. The sample size of 38 patients is too small to make definite conclusions, there were no repeated measurements and no control group. A sweat chloride test was not part of the standard care of adult patients with cystic fibrosis in Germany and was therefore not available for the analysis.

CONCLUSIONS

Triple CFTR modulation therapy and airway clearance techniques improve airway resistance and pulmonary gas trapping. This is reliably assessed by measuring sRAWeff, which is associated with exercise capacity. Future studies should incorporate body plethysmography to understand their relationship, especially if FEV_1 does not improve after therapy initiation.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported. D. Dieninghoff reports receiving consulting fees from Chiesi, VERTEX and payments for lectures from Chiesi, VERTEX and FOMF. W. Windisch reports grants from Löwenstein Medical, Philips/Respironics and GCI for his institution. He also reports receiving personal consulting fees BioNTech Europe GmbH and personal payments for lectures from AstraZeneca, Sentec, Chiesi, Boehringer Ingelheim, Novartis, BioNTech Europe GmbH and Philips/Respironics.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Ethics Committee of Witten/Herdecke University (Approval number: S-181/2022; Date: 27 September 2022). This was a retrospective study so patients' informed consent was not required.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS

MW-S, WW and MPB: led conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing of original draft, and reviewing and editing of the manuscript. DD, TM, SBS, WW and C-PC: contributed to conceptualization, data curation, formal analysis, methodology, project administration, resources, software, validation, visualization and reviewing and editing of original draft. DD: contributed especially to data curation, investigation, and validation of the data. TM: contributed especially to the formal analysis and methodology. All authors read and approved the final version of the manuscript.

PROVENANCE AND PEER REVIEW

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