Dual and triple modulator therapy for chronic rhinosinusitis in cystic fibrosis patients*

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Abstract

Background: The introduction of CFTR modulators has changed the landscape in the treatment of cystic fibrosis (CF) and early case series have shown improvements in sinonasal outcomes in this patient population.

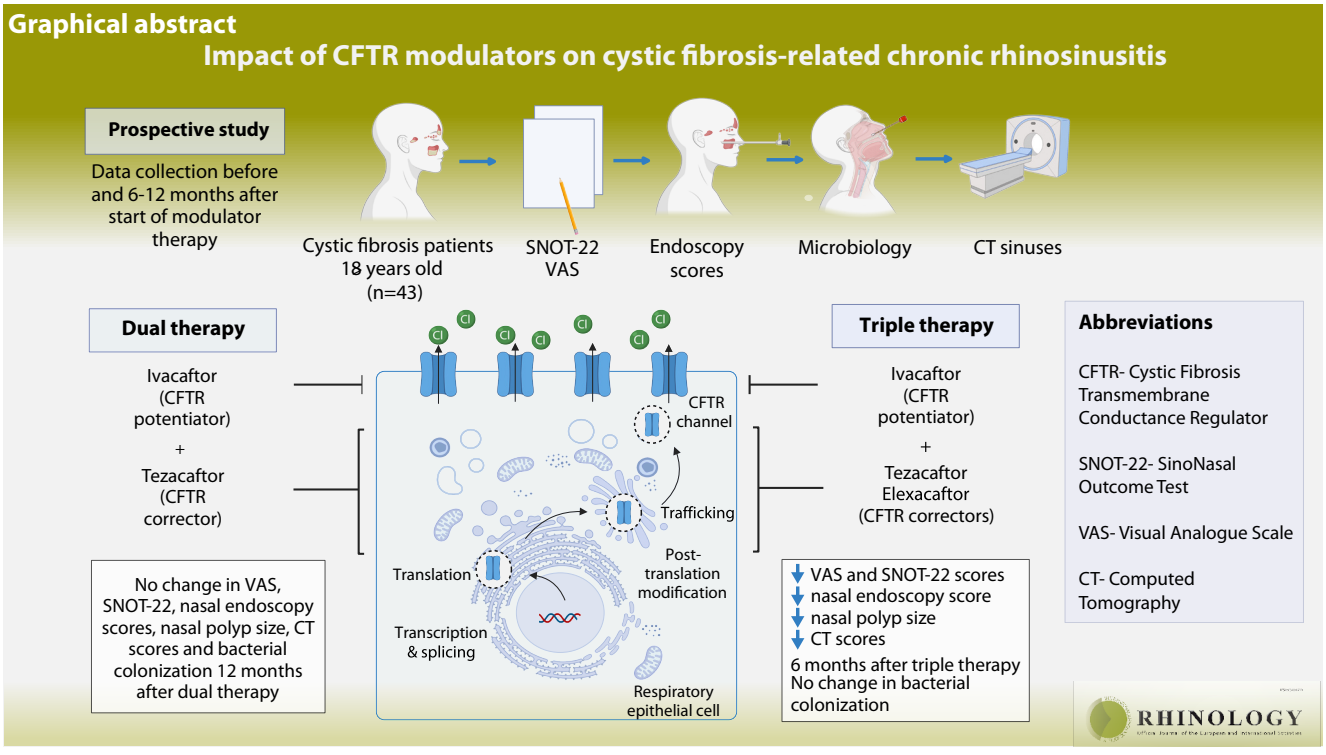
Methodology: A real-word data study was performed to evaluate the impact of dual therapy with tezacaftor/ivacaftor (TEZ/IVA) and triple therapy with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on CF-related chronic rhinosinusitis (CRS), by comparing subjective and objective outcome measures at baseline, 12 months after treatment with TEZ/IVA and six months after treatment with ELX/TEZ/IVA.

Results: In total, 43 CF patients, with a mean age of 32 years, were included. After triple therapy, significant improvements in overall visual analogue scale, SNOT-22, Lund Kennedy, nasal polyps, and Lund-Mackay scores were observed, whereas no beneficial effect could be seen in patients treated with dual therapy. Bacterial upper airway colonization did not differ pre- and post-modulator therapy in the present study. The number of responders to dual and triple therapy is 23.8% and 63.2% of the patients, respectively.

Conclusions: Triple therapy with ELX/TEZ/IVA is superior to dual therapy with TEZ/IVA in the treatment of CF-CRS, as significantly reduced sinonasal complaints, nasal endoscopy and CT scores were observed after triple therapy, whereas this was not the case for dual therapy.

Key words: CFTR, chronic rhinosinusitis, CRS, cystic fibrosis, modulator

Graphical abstract



Introduction

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators, small molecules that are able to restore the functionality of the impaired CFTR channel in cystic fibrosis (CF) patients, were approved in Europe in 2012 and have been changing lives of CF patients ever since (1). CFTR modulators are usually classified in two subgroups: CFTR potentiators and correctors. Potentiators (e.g. ivacaftor) improve ion transport at the level of the plasma membrane, whereas correctors (e.g. lumacaftor, tezacaftor and elexacaftor) improve CFTR processing and trafficking to the plasma membrane [(1)]. The exact molecular mechanisms of action of these modulators remain unknown.

In Europe, four modulators have been approved for use in CF patients: ivacaftor in monotherapy (IVA, marketed under trade name Kalydeco®), combination treatment of ivacaftor with tezacaftor (TEZ/IVA, marketed under trade name Symkevi/Kalydeco®), ivacaftor with lumacaftor (LUM/IVA, marketed under trade name Orkambi®) and triple combination of ivacaftor with tezacaftor and elexacaftor (ELX/TEZ/IVA, marketed under trade name Kaftrio®) [(2-4)]. In Belgium, reimbursement of TEZ/IVA was approved in 2021 for patients with at least one gating mutation (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R) [(5)]. Reimbursement for ELX/TEZ/IVA has been available since September 2022, for patients with at least one ΔF508 mutation [(6)].

Both randomized controlled trials and real-world data studies have shown that modulators significantly improve pulmonary function, nutritional status, quality of life and sweat chloride, compared to placebo. Furthermore, these modulators decrease lower airway colonization with *Pseudomonas aeruginosa* and *Staphylococcus aureus* and secondary reduce the number of intravenous antibiotic courses and need for maintenance treatments (including long-term macrolides and dornase alfa) [(7-10)].

Shortly after the introduction of IVA, the first reports indicated not only amelioration in pulmonary health but also notable improvements in cystic fibrosis-related secondary chronic rhinosinusitis (CRS), especially in patients with at least one G551D gating mutation [(11)]. Studies on ELX/TEZ/IVA, both prospective and retrospective, revealed substantial reductions in sinonasal complaints and radiographical disease severity [(12-19)]. To date, no clinical data are available on the impact of TEZ/IVA dual therapy on CF-related secondary CRS or the effect of modulator therapy on nasal endoscopy or bacterial upper airway colonization.

As CFTR modulators are increasingly being recognized as the 'golden standard' for CF treatment, post-market real-world data studies are needed to provide important long-term data on the safety and effectiveness of these modulators. The main goal of the present study is to assess the impact of dual TEZ/IVA therapy and triple ELX/TEZ/IVA therapy on CF-related secondary chronic rhinosinusitis in the adult CF population at our tertiary hospital.

Materials and methods

Data collection

A monocenter, real-world data study was performed, between January 2020 and October 2023, to evaluate the impact of dual and triple modulator therapy on CF-CRS. At our center, an annual rhinological evaluation by an ENT specialist at the Pneumology outpatient clinic is implemented in the standard-of-care follow-up scheme of CF patients. During this rhinological evaluation, a nasal endoscopy, a sinonasal swab and a CT scan of the sinuses are performed once a year to evaluate the objective severity of CF-CRS. Furthermore, to assess the subjective impact on quality of life of CF-CRS, patients are asked to fill-in questionnaires.

First, a nasal endoscopy, using a rigid 4 mm 30° nasal endoscope, is performed and scored using Lund-Kennedy (score from 0 to 12, Appendix 1) and Modified Davos (score from 0 to 8, Appendix 2) scores. Moreover, a sinonasal swab is performed at the level of the middle meatus, on the side with visually the most pathology, bacterial cultures are grown, and antibiotic sensitivity is assessed. The latter are performed at the Clinical Department of Laboratory Medicine (UZ Leuven) according to CF protocols. Furthermore, a low-dose CT of the sinuses, without intravenous contrast, is performed and scored using the Modified Lund-Mackay scoring system (score from 0 to 24, Appendix 3). Lastly, patients are asked to fill-in a questionnaire, including the SNOT-22 score (score from 0 to 110, Appendix 4) and visual analogue scale (VAS) scores, from 0 to 100mm, on overall sinonasal symptoms, nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, and sense of smell (Appendix 5). Additional data on demographics, rhinological history, and current treatments, and CF genotype and phenotype are collected.

To evaluate the impact of dual and triple therapy on CF-CRS, both objectively and subjectively, data from three consecutive years were collected. In 2020, baseline data were gathered, before the start of modulator therapy. From April 2022 on, ± 12 months after reimbursement of TEZ/IVA in Belgium, outcome measures were repeated to evaluate the impact of dual modulator therapy, and from March 2023 on, ± six months after the reimbursement of ELX/TEZ/IVA in Belgium, data were collected for the last time to evaluate the impact of triple modulator therapy on CF-CRS. Data were stored in a server protected RedCap database.

Lastly, the rate of patients responding – both subjectively and objectively – to modulator therapy was measured based on

SNOT-22 (questionnaire) and Modified Lund-Mackay (CT) scores. A minimal clinically important difference (MCID) was defined, to make a distinction between statistically and clinically significant changes in outcome measures. A MCID in SNOT-22 score was defined as a change in score of >12 points [20], and a MCID in Modified Lund-Mackay score was defined as a change in score of >5 points [21].

The study was approved by the Ethical Committee of UZ/KU Leuven and written informed consent was obtained from all included patients.

Sample size calculation

Sample size calculation was performed to obtain an adequate statistical power to detect significant differences in outcome measures. The analysis was performed using G*Power software (version 3.1.9.7.) and was designed to accommodate paired data analysis with a two-sided test, an alpha (significance) level of 0.05, and a desired statistical power of 90%. The Modified Lund-Mackay score was used as outcome parameter to build the power calculation, as previous literature has shown that patient-reported outcome measures poorly correlate with objective disease extent [22].

For the subgroup of patients treated with ELX/TEZ/IVA, the estimated sample size was nine, based on the change in mean Lund-Mackay score of -3.6 after six months of treatment as reported by Beswick et al. [12].

Prior to this study, no (pilot)data were available for the TEZ/IVA subgroup. Consequently, the power analysis was conducted using the baseline Modified Lund-Mackay scores from our pre-existing patient registry, which consisted of 122 patients with a mean score of 11.69 and a standard deviation of 6.31 [22]. To detect a MCID of >5, power analysis revealed an estimated sample size requirement of 19 participants for this specific subgroup.

Statistical analysis

Data analysis was performed using GraphPad Prism software (version 9.4.1.). Descriptive data, including mean and standard deviation (SD) for quantitative data with a Gaussian distribution, and median and interquartile range for skewed data, were calculated. The normality of data was assessed by the Shapiro-Wilk and Anderson-Darling test.

Differences in continuous baseline characteristics, between the subgroup of patients treated with dual and the subgroup of patients treated with triple modulator therapy, were assessed using an unpaired t-test for normally distributed data and Mann-Whitney test for skewed data. Differences in categorical characteristics were compared using the χ^2 test.

The effect of CFTR modulators was assessed by comparing subjective (VAS, SNOT-22) and objective (Lund-Kennedy, Modified Davos and Modified Lund-Mackay) scores at baseline and after modulator treatment, using a paired t-test or one-way ANOVA (or mixed effects model in case of missing data) – in case of normally distributed data – and using a Wilcoxon matched-pairs signed rank test or Friedman test – in case of skewed data. Multiple testing was corrected using the built-in Dunn–Šidák correction.

For all statistical tests, differences between the means were calculated and a 95% confidence (CI) interval was established. The difference was considered statistically significant when p-values were < 0.05 (two-sided testing).

Results

Demographical data

Between January 1st 2020 and October 1st 2023, 43 adult CF patients were included, of which 26 males and 17 females with a mean age of 32 (SD ± 9) years at inclusion. The majority of the patients were homozygous for the ΔF508 mutation (70%), the remaining patients were heterozygous for the ΔF508 mutation. At inclusion, the mean BMI, FEV1% and sweat chloride were 22.3 (SD ± 1) kg/m^2, 73.4 (SD ± 17)% and 105 (SD ± 15) mmol/L, respectively.

Out of 43 patients, data were available from 25 patients both at baseline and after receiving dual therapy with TEZ/IVA, with an average treatment duration of 14 months (SD ± 2.5). Additionally, baseline and post-ELX/TEZ/IVA treatment data were gathered from 39 patients, with an average treatment duration of 8 months (SD ± 2). No significant baseline and demographic differences were observed in the subgroup of patients treated with TEZ/IVA and ELX/TEZ/IVA (Table 1).

Within the TEZ/IVA treatment subgroup, one patient was treated with lumacaftor prior to dual treatment, and one patient with ivacaftor in monotherapy. The remaining patients (92%) did not receive modulator therapy prior to start of dual therapy. In contrast, in the ELX/TEZ/IVA treatment subgroup, 29 patients (74%) had received prior dual therapy with TEZ/IVA before starting triple therapy. Longitudinal data was available from 20 patients, receiving dual therapy first, followed by triple therapy.

Subjective outcome measures (VAS and SNOT-22 score)

No significant differences in mean VAS scores for total sinonasal symptom were observed after treatment with dual TEZ/IVA therapy (Figure 1A, Table 2). Moreover, for the cardinal sinonasal symptoms (nasal obstruction, postnasal drip, rhinorrhea, facial pain/pressure, and reduced smell), no significant reductions in VAS score were observed compared to baseline (Table 2).

Table 1. Comparison in demographics and baseline characteristics in the subgroup of patients treated with tezacaftor/ivacaftor (TEZ/IVA) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA).

Outcome parameter	Subgroup TEZ/IVA (n=25)	Subgroup ELX/TEZ/IVA (n=39)	p-value	95% CI
Age (mean ± SD)	30 ± 9 years	32 ± 10 years	0,9581	[-5.8;9.5]
Gender (n, %): Male / Female	14 (56%)/ 11 (44%)	25 (64%)/ 14 (36%)	0,6030	[0.6;1.3]
BMI at inclusion (mean ± SD)	23.5 ± 3 kg/m^2	23.6 ± 3 kg/m^2	>0.9999	[-7.6;7.7]
Sweat chloride at inclusion (mean ± SD)	104.9 ± 14.1 mmol/L	103.5 ± 16.7 mmol/L	0,9900	[-10.3;7.4]
FEV1% at inclusion (mean ± SD)	77.5 ± 13.2 %	73.0 ± 17.3 %	0,4407	[-12.2;3.1]
Genotype (n, %) :				
ΔF508 homozygous	22 (66.7%)	26 (65%)	>0,9999	[0.7;1.4]
ΔF508 heterozygous	11 (33.3%)	14 (35%)		
Days of antibiotics in 6 months prior to inclusion (mean ± SD)				
Oral antibiotics	27 ± 44 days	12 ± 29 days	0,1158	[-32.7;3.7]
IV antibiotics	10 ± 30 days	3 ± 7 days	0,1723	[-16.7;3.1]
Local antibiotics	2 ± 5 days	0.5 ± 2 days	0,2147	[-2.9;0.7]
Anti-inflammatory antibiotic (yes/no) (n, %)	18 (72%)/ 7 (28%)	28 (76%)/ 9 (24%)	0,7743	[0.7;1.3]
Intranasal treatment (yes/no) (n,%)				
saline irrigations	8 (35%)/ 15 (65%)	8 (22%)/ 29 (78%)	0,3688	[0.7;3.6]
corticosteroid	12 (52%)/ 11 (48%)	14 (38%)/ 23 (62%)	0,2981	[0.8;2.4]
Previous FESS before modulator (yes/no) (n, %)	12 (52%)/ 11 (48%)	16 (41%)/ 23 (59%)	0,4375	[0.7;2.2]

Abbreviations: n= number, TEZ/IVA= tezacaftor/ivacaftor, ELX/TEZ/IVA= elexacaftor/ivacaftor/tezacaftor, SD= standard deviation, CI= confidence interval, BMI= body mass index, FEV1% = forced expiratory volume in one second, IV= intravenous, FESS= functional endoscopic sinus surgery.

Table 2. Differences in subjective and objective outcome measures before and after treatment with tezacaftor/ivacaftor (TEZ/IVA) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA).

	Baseline before modulator	After treatment with TEZ/IVA (n=25)			After treatment with ELX/TEZ/IVA (n=39)		
Outcome parameter	Mean ± SD	Mean Δ	95% CI	p-value	Mean Δ	95% CI	p-value
VAS total symptom (mm)	32.5 ± 28.8	-3.4	[-17.9;11.1]	0.8156	-10.3	[-18.5;-2.2]	**0.0011***
VAS nasal obstruction (mm)	28.0 ± 28.6	2.4	[-13.9;18.8]	0.9964	-4.4	[-18.9;4.4]	0,6338
VAS postnasal drip (mm)	30.0 ± 29.8	-2.29	[-13.4;8.8]	0.9843	-11.6	[-18.8;-4.4]	**0.0005***
VAS anterior rhinorrhea (mm)	23.5 ± 21.1	-2.5	[-19.1;14]	0.9959	0.2	[-8.6;9.0]	>0.9999
VAS facial pain (mm)	31.2 ± 29.1	-7.1	[-20.5;6.4]	0.5556	-3.1	[-13.2;7.1]	0.9328
VAS reduced smell (mm)	20.8 ± 25.6	3.8	[-5.8;13.4]	0.7938	2.0	[-6.0;10.2]	0.9328
SNOT-22 score	24.4 ± 15.2	-0.53	[-9.2;8.1]	0.9861	-6.8	[-12.8;-0.7]	**0.0254***
Lund-Kennedy score	5.9 ± 3	-0.7	[-1.9;0.6]	0.3987	-1.6	[-2.6;-0.6]	**0.0017***
Modified Davos score	1.4 ± 1.9	-0.3	[-1.4;0.8]	0.7329	-0.8	[-1.4;-0.1]	**0.0171***
Modified Lund-Mackay score	13.1 ± 6.2	-0.7	[-3.6;2.2]	0.8137	-6.3	[-8.1;-4.4]	**<0.0001***
Presence of pathogenic bacteria (n,%)	22/48 (46%)	6/14 (43%)	RR 0.8333 [0.3;2.1]	>0,9999	11/34 (32%)	RR 1.545 [0.9;2.8]	0,2177

Abbreviations: n=number, TEZ/IVA= tezacaftor/ivacaftor, ELX/TEZ/IVA= elexacaftor/tezacaftor/ivacaftor, SD= standard deviation, Δ=change, CI= confidence interval, VAS= visual analogue scale, SNOT-22= sinonasal outcome test-22, RR= relative risk. * p-values <0.05 are considered statistically significant.

After treatment with ELX/TEZ/IVA, a statistically significant reduction in VAS score for total sinonasal symptom of -10.3 mm (p=0.0011) was observed (Figure 1A, Table 2). Additionally, a significant reduction in VAS score for postnasal drip was objectified

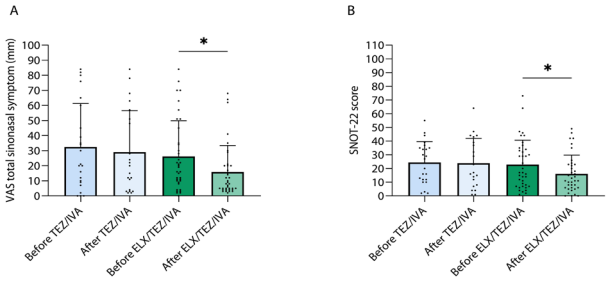


Figure 1. Mean visual analogue scale (VAS) scores for total sinonasal symptom (A) and SNOT-22 scores (B) before, and after treatment with tezacaftor/ivacaftor (TEZ/IVA) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). * indicating a statistically significant difference with p-value <0.05.

(mean change= -11.6 mm, p=0.0005). No significant changes were noted for the remaining cardinal sinonasal symptoms (Table 2).

In regard to the SNOT-22 score, a significant reduction of -6.8 points (p=0.0254) was observed, compared to baseline, after treatment with ELX/TEZ/IVA, whereas no differences could be achieved after treatment with TEZ/IVA (Figure 1B, Table 2).

Nasal endoscopy

After treatment with dual TEZ/IVA therapy, no changes in Lund-Kennedy and Modified Davos scores could be observed. In contrast, a significant reduction in Lund-Kennedy and Modified Davos scores of -1.6 (p=0.0017) and -0.8 points (p=0.0171), respectively, were noted after ELX/TEZ/IVA treatment (Figure 2, Table 2).

CT scan

In alignment with the endoscopy findings, a statistically significant decrease of 6.3 points (p<0.0001) in Modified Lund-Mackay scores was seen following ELX/TEZ/IVA treatment, whereas no differences were noted after treatment with TEZ/IVA (Figure 2-3, Table 2).

Bacteriology

In the subgroup of patients treated with dual therapy, longitudinal microbiology data, from the upper airways, are available from 14 out of 25 patients. At baseline, five patients were colonized intranasally with *S. aureus*. After dual therapy, two patients (2/5) with previous *S. aureus* colonization were eradicated, while three patients had persisting presence of *S. aureus*. Notably, among the nine patients who had not been previously colonized with pathogenic bacteria, three acquired new colonizations with *S. aureus* after commencing dual therapy.

Furthermore, longitudinal microbiology data were available from 34/39 patients treated with ELX/TEZ/IVA. Seventeen out of 34 patients were colonized with pathogenic bacteria intranasally at baseline, including *Stenotrophomonas* spp. in one patient, *Staphylococcus epidermidis* in one patient, *P. aeruginosa* in two patients and *S. aureus* in thirteen patients. Eradication after triple modulator therapy was seen in 11/17 patients and persistence of the pathogenic bacteria in the remaining patients. In five out of 17 patients without prior presence of pathogenic bacteria, *S. aureus* could be isolated from the nasal cavity.

Statistically, no differences in number of patients colonized with/without pathogenic bacteria could be found after dual or triple therapy, compared to baseline (Table 2).

Rhinological and antibiotic treatments

Before the start of modulator therapy, 35.7% (15/42) of the patients performed daily nasal irrigations and 47.6% (20/42) applied intranasal corticosteroids on a daily basis. After triple therapy with ELX/TEZ/IVA, no changes were seen in the chronic use of nasal irrigations (mean change= -11.7%, p=0.3097) and intranasal corticosteroids (mean change=-6.5%, p=0,6469). No differences in use of oral (mean change=-1 day, p=0.8955),

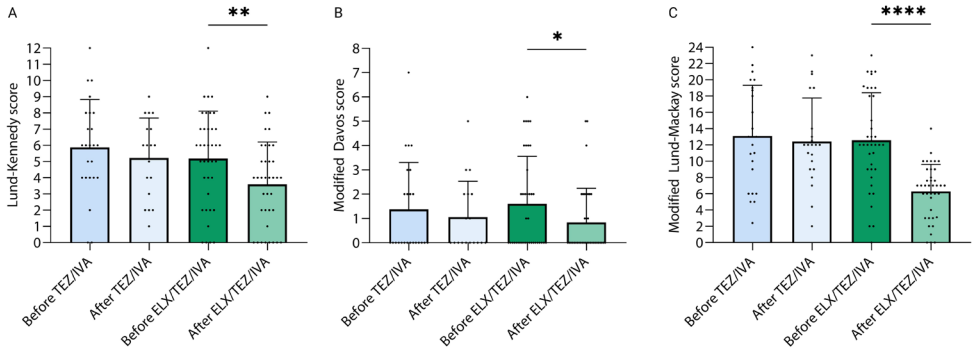


Figure 2. Comparison in mean Lund-Kennedy (A), Modified Davos (B) and Modified Lund-Mackay (C) scores at baseline, and following treatment with tezacaftor/ivacaftor (TEZ/IVA) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). * indicating a statistically significant difference with p-value <0.05.

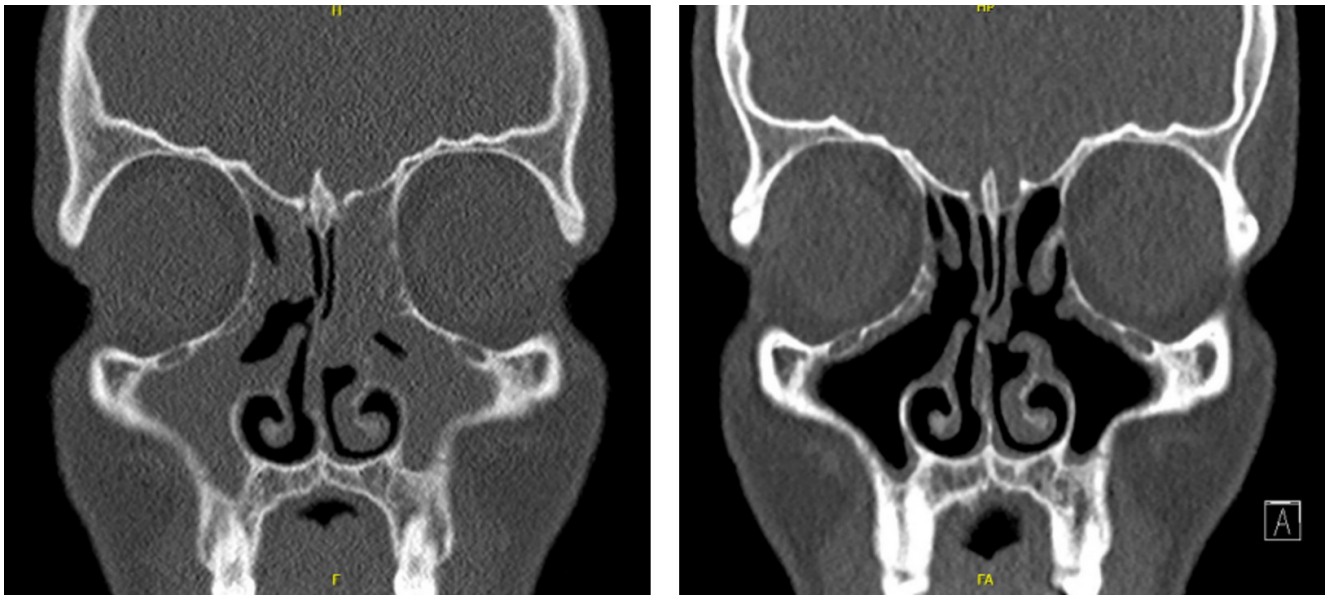


Figure 3. CT sinuses without intravenous contrast of homozygous ΔF508 patient before (left) and after (right) treatment with elexacaftor/tezacaftor/ivacaftor for six months, with reduction in opacification at the levels of the maxillary and ethmoidal sinuses and reduction of Modified Lund-Mackay score from 19/24 (left) to 2/24 (right).

intravenous (mean change=-8.5 days, p=0.2088), local (mean change=3 days, p=0.1624) or anti-inflammatory (mean change= -6.3%, p=0.6125) antibiotics could be observed after treatment with dual therapy, compared to baseline. Similar findings were observed after treatment with triple therapy: no significant reduction in number of treatment days with oral (mean change= -8.9 days, p=0.0875), local (mean change=-0.5 days, p=0.1600) and anti-inflammatory (mean change= -3.7%, p=0.6086) antibiotics could be found. Nevertheless, a significant reduction in number of days of intravenous antibiotics was seen six months after the start of triple therapy (mean change= -3.3 days, p=0.0048).

Longitudinal data

Longitudinal data was collected from 20 patients, receiving dual therapy first for ±12 months, followed by triple therapy for ±six months (Figure 4).

First, no significant changes were observed in SNOT-22 after dual therapy with TEZ/IVA compared to baseline (mean change= -2.96, 95% CI[-11.2;5.3], p=0.6280). In contrast, a significant reduction was seen after treatment with ELX/TEZ/IVA in comparison to baseline (mean change=-9, 95% CI[-16.6;1.4], p=0.0192). No differences in SNOT-22 score could be observed between dual and triple therapy.

Second, significantly lower Modified Lund Mackay scores were observed after treatment with triple therapy, compared to baseline (mean change=-7.35, 95% CI[-11;-3.7], p=0.0002) and to dual therapy (mean change=-5.9, 95% CI[-8.9;-2.9], p=0.0003). No changes were observed after treatment with dual therapy, compared to baseline.

Rate of responders

In the TEZ/IVA treated subgroup, only 10.5% of the patients had a change in SNOT-22 of > 12. Moreover, in the ELX/TEZ/IVA subgroup, 22.2% of the patients had a clinically important difference in SNOT-22. A MCID in Modified Lund-Mackay score was observed in 23.8% and 63.2% of the patients treated with dual and triple therapy, respectively.

Discussion

CFTR modulators, especially the highly effective triple combination of ELX/TEZ/IVA, have dramatically reduced disease burden in CF-patients and from early-on, data on the impact of modulator therapy on CF-related secondary CRS have been reported. The aim of the present study was to compare efficacy of dual and triple therapy in the treatment of CF-CRS in a real-world data setting. The latter meaning that data are collected over time in patients treated with modulators according to standard-of-care treatment regimen, as proposed by the treating Pulmonologists, and depending on reimbursement criteria in Belgium. Data are collected during routine ENT consultations instead of fixed study visits.

Our data showed that ELX/TEZ/IVA significantly reduces sinonasal symptoms and CT scores, compared to baseline. These findings are in line with previously performed observational

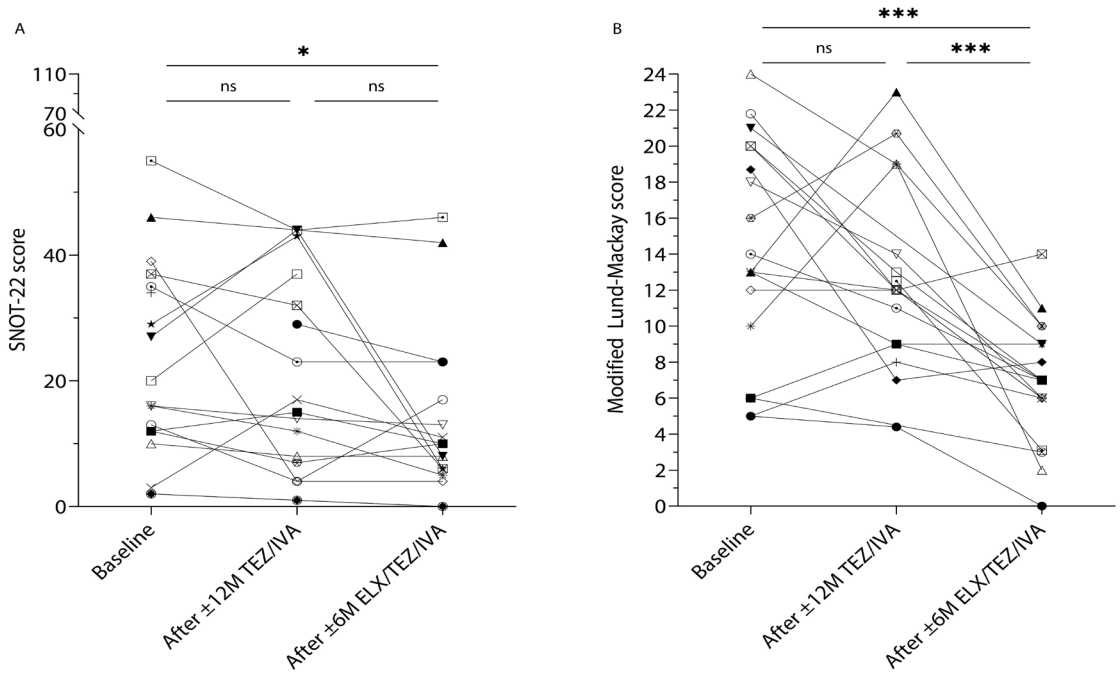


Figure 4. Longitudinal evaluation of SNOT-22 (A) and Modified Lund-Mackay (B) scores at baseline, ±12 months after start of dual therapy with tezacaftor/ivacaftor (TEZ/IVA) and ±6 months after treatment with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). * indicating a statistically significant difference with p-value <0.05.

studies, showing that ELX/TEZ/IVA significantly reduces SNOT-22 [12-16,18-19] and Lund-Mackay scores [12-13, 17, 19]. It should be noted that the magnitude of reduction in SNOT-22 score of -6.8 points is rather limited in comparison to current literature, with a reported mean change in SNOT-22 score ranging from -10.5 to -15 (12-16,18-19), and might not be clinically meaningful. This might be due to low SNOT-22 scores at baseline (24.4 ± 15.2 points). Moreover, a statistically significant reduction in VAS score for total sinonasal symptom was observed, but when looking at the VAS scores for individual sinonasal symptoms, only a significant reduction could be observed for postnasal drip. No major improvements in nasal patency, sense of smell, facial pain/pressure or anterior rhinorrhea could be observed. But as was the case for the SNOT-22 score, baseline VAS scores were low with a mean score of 32.5 ± 28.8 mm.

Furthermore, our data revealed significantly lower nasal endoscopy (Lund-Kennedy) and nasal polyp scores (Modified Davos) after treatment with ELX/TEZ/IVA. Only one other prospective study reported data on nasal endoscopy appearances, using the Lund-Kennedy score, without looking at specific nasal polyp scores [13].

For dual therapy with TEZ/IVA, no significant changes in subjective or objective outcome parameters could be observed, compared to baseline. Therefore, dual therapy is inferior to triple therapy in the treatment of CF-CRS. To date, this is the first study reporting clinical rhinological data after TEZ/IVA treatment, and therefore comparison with previous literature is difficult. Previous literature on IVA in monotherapy, in patients with specific gating mutations (G551D or SN1251N), did show significant changes in CT and nasal endoscopy scores [11, 23]. McCormick et al. did see a significant reduction in SNOT-20 score after IVA treatment in 151 patients with at least one G551D mutation, but less than the pre-specified minimal clinically important difference, also due to low baseline values [24]. IVA is a CFTR potentiator that improves the gating function of the CFTR channel and is therefore useful in patients with a gating defect (class III mutations) [1]. Class III or gating mutations are defined as mutations in the CFTR gene in which sufficient CFTR protein reaches the plasma membrane, but the gating of the ion channel is impaired and does not function [1]. The lower efficacy rates in our cohort might be due to the absence of patients carrying these specific gating mutations. Eighty-eight % of the patients in the TEZ/IVA subgroup were homozygous for ΔF508, which is representative for the general population. The ΔF508 mutation is defined as a class II mutation, in which the CFTR protein is misfolded and cannot reach the cell surface [1]. The remaining of the patients in our cohort were heterozygous for ΔF508, with one patient carrying a class I (no production of functional CFTR) and two patients carrying a class V mutation (insufficient quantity of

CFTR channels at the plasma membrane). Nevertheless, studies did show that TEZ/IVA significantly improves lung function in ΔF508 homozygous or heterozygous patients [25, 26], but also for pulmonary outcomes it has been shown that these effects are smaller than seen when treating patients with specific G551D mutations in monotherapy [27]. No demographical or baseline (e.g. age, gender, disease severity, previous medical/surgical treatments, genotype) differences between both subgroups could be observed that might explain the difference in efficacy. We hypothesize that the additional effect seen with triple therapy is due to adding a second CFTR corrector elexacaftor, that facilitates folding and translocation of the CFTR protein to the plasma membrane.

The impact of modulator therapy on bacterial upper airway colonization was investigated by repeatedly culturing sinonasal swabs, harvested at the level of the middle meatus. For both subgroups, no significant differences in number of patients colonized with pathogenic bacteria could be observed. Gostelie et al. analyzed nasopharyngeal swabs in four patients, with presence of *P. aeruginosa* (n=3) and *S. aureus* (n=1) at baseline and eradication in 3 out of 4 after 18 months [23]. As current literature regarding impact of modulator therapy on upper airway colonization and the sinonasal microbiome remains limited, future studies could potentially elucidate this.

To determine the rate of responders in our treatment cohorts, a MCID in SNOT-22 and Modified Lund-Mackay score were defined. A clinically meaningful reduction in sinonasal symptoms was seen in 10.5% and 22.2% of the patients treated with TEZ/IVA and ELX/TEZ/IVA, respectively. On CT, a clinically important reduction was observed in 23.8% and 63.2% of the patients treated with dual and triple therapy, respectively. On one hand, these data indicate that especially triple therapy is effective in the treatment of CF-related CRS. Until now, very little data is available on how the introduction of CFTR modulators would affect clinical practice in terms of systematic ENT follow-up in this patient population, imaging necessity, continuation of maintenance medication (including corticosteroid spray or nasal irrigations), etc. Further research is needed on this topic with the goal of formulating updated guidelines that align with the advancements brought by CFTR modulators. On the other hand, there is still a proportion of the patients that does not fully respond to modulator treatment. For these patients, treatment alternatives should still be sought to improve sinonasal outcomes.

The main limitation of this study is its observational design. Previous clinical trials have already extensively studied the effect of ELX/TEZ/IVA and IVA in monotherapy on CF-CRS, and for this subgroup of patients our real-world data offers valuable insights in a more realistic setting. Nevertheless, as this was the first study evaluating the effect of TEZ/IVA, we could not compare our results with existing randomized controlled trials. As the data are, inherently due to the study design, influenced by treatment adherence and compliance, heterogeneity in our patient population with different underlying genotypes and disease severity, and variability in use of maintenance medication for CF-CRS, the effects of TEZ/IVA might be underestimated. Performing a randomized controlled trial with TEZ/IVA would be beneficial to gain more insights in the mechanisms of action of dual therapy, however as triple therapy is now considered the golden standard such study is no longer ethically accepted.

Conclusion

Triple therapy with elexacaftor/tezacaftor/ivacaftor significantly improves sinonasal symptoms and reduces objective disease severity on nasal endoscopy and CT scan. Dual therapy with tezacaftor/ivacaftor is inferior to triple therapy as no changes could be observed in comparison to baseline. Objectively, 63.2% and 23.8% of the patients with CF-related CRS respond to triple and dual therapy, respectively. No changes in bacterial upper airway colonization could be observed and future studies on this topic are recommended.

Authorship contribution

SU: conceptualization, methodology, investigation, data curation, formal analysis, writing-original draft, visualization, project administration; CC: data curation, formal analysis, writing, review and editing, MJ: writing, review and editing, LD: conceptualization, co-supervision, writing, review and editing, LVG: conceptualization, methodology, resources, supervision, formal analysis, project administration, funding acquisition, writing, review and editing. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

We have no conflicts of interest to declare.

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SUPPLEMENTARY MATERIAL

Appendix 1. Lund-Kennedy scoring system.

Characteristic	Severity (0,1,2)
Polyps, left	0= absent, 1= only in middle meatus, 2= beyond middle meatus
Polyps, right	0= absent, 1= only in middle meatus, 2= beyond middle meatus
Edema, left	0= absent, 1= mild, 2= severe
Edema, right	0= absent, 1= mild, 2= severe
Discharge, left	0= no discharge, 1= clear, thin discharge, 2= thick, purulent discharge
Discharge, right	0= no discharge, 1= clear, thin discharge, 2= thick, purulent discharge
Total score	Score ranging from 0 to 12 out of 12

Appendix 2. Modified Davos scoring system.

Polyp Score (left, right)	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity
Total Modified Davos score	Score ranging from 0-8 (left and right combined)

Appendix 3. Lund-Mackay and Modified Lund Mackay scoring system.

Characteristic	Severity (0,1,2)
Maxillary sinus, left	0= no abnormality, 1= partial opacification, 2= total opacification
Maxillary sinus, right	0= no abnormality, 1= partial opacification, 2= total opacification
Anterior ethmoid, left	0= no abnormality, 1= partial opacification, 2= total opacification
Anterior ethmoid, right	0= no abnormality, 1= partial opacification, 2= total opacification
Posterior ethmoid, left	0= no abnormality, 1= partial opacification, 2= total opacification
Posterior ethmoid, right	0= no abnormality, 1= partial opacification, 2= total opacification
Frontal sinus, left	0= no abnormality, 1= partial opacification, 2= total opacification
Frontal sinus, right	0= no abnormality, 1= partial opacification, 2= total opacification
Sphenoid sinus, left	0= no abnormality, 1= partial opacification, 2= total opacification
Sphenoid sinus, right	0= no abnormality, 1= partial opacification, 2= total opacification
Ostiomeatal complex, left	0= not obstructed, 2= obstructed
Ostiomeatal complex, right	0= not obstructed, 2= obstructed
Total score	Score ranging from 0 to 24 out of 24
Modified Lund-Mackay score	Lund Mackay score x 24 / (24- 2x number of aplastic sinuses)

Appendix 4. 22-item Sinonasal Outcome Test (SNOT-22).

	No problem	Very mild problem	Mild or slight problem	Moderate problem	Severe problem	Problem as bad as it can be	Most important
Need to blow nose	0	1	2	3	4	5	O
Sneezing	0	1	2	3	4	5	O
Runny nose	0	1	2	3	4	5	O
Cough	0	1	2	3	4	5	O
Post nasal discharge	0	1	2	3	4	5	O
Thick nasal discharge	0	1	2	3	4	5	O
Ear fullness	0	1	2	3	4	5	O
Dizziness	0	1	2	3	4	5	O
Ear pain	0	1	2	3	4	5	O
Facial pain/pressure	0	1	2	3	4	5	O
Difficulty falling asleep	0	1	2	3	4	5	O
Waking up at night	0	1	2	3	4	5	O
Lack of a good night's sleep	0	1	2	3	4	5	O
Waking up tired	0	1	2	3	4	5	O
Fatigue	0	1	2	3	4	5	O
Reduced productivity	0	1	2	3	4	5	O
Reduced concentration	0	1	2	3	4	5	O
Frustrated/ restless/ irritable	0	1	2	3	4	5	O
Sad	0	1	2	3	4	5	O
Embarrased	0	1	2	3	4	5	O
Sense of taste/smell	0	1	2	3	4	5	O
Blockage/congestion of nose	0	1	2	3	4	5	O
Subtotal	_____	_____	_____	_____	_____	_____	
Total score	_____						

Appendix 5. Visual Analogue Scale (VAS) scores.