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Dose adjustments of Elexacaftor/Tezacaftor/Ivacaftor in response to mental health side effects in adults with cystic fibrosis

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ABSTRACT

Introduction: Deterioration in mental health has been reported in a minority of individuals with cystic fibrosis starting elexacafor/tezacaftor/ivacaftor (ELX/TEZ/IVA). We report our experience of using sweat chloride and markers of clinical stability to titrate dose reduction with the aim of minimising adverse events and maintaining clinical stability.

Method: Adults (n = 266) prescribed ELX/TEZ/IVA, were included. Adverse events, sweat chloride, lung function and clinical data were collected.

Results: Nineteen (7.1%) individuals reported anxiety, low mood, insomnia and "brain fog" with reduced attention and concentration span. Thirteen underwent dose reduction with sweat chloride remained normal (<30 mmol L-1) or borderline (30–60 mmol L-1) in six (46.2%) and seven (53.2%) cases respectively. Improvement or resolution of AEs occurring in 10 of the 13 cases.

Conclusion: Dose adjustment of ELX/TEZ/IVA was associated with improvement in mental health AEs without significant clinical deterioration. Sweat chloride concentration may prove useful as a surrogate marker of CFTR function.

1. Introduction

The introduction of elexacaftor, tezacaftor and ivacaftor (ELX/TEZ/IVA) in clinical practice has been life changing for many people with cystic fibrosis (CF). This triple combination of cystic fibrosis transmembrane conductance regulator (CFTR) modulators has proved highly effective at increasing CFTR function in people homozygous or heterozygous for the F508del mutation [1–3].

In clinical trials, treatment with ELX/TEZ/IVA has resulted in a significant reduction in pulmonary exacerbations and improved lung function and quality of life [1–3]. The drug combination was also well tolerated, with minimal adverse events. Real-world experience, however, would suggest that a wider range of previously under-reported adverse events (AEs) including insomnia, anxiety, mental fogginess and deterioration in mental health might occur [4–6]. To date the literature is limited to three reports of ELX/TEZ/IVA being associated with mental health AEs [4–6].

This may simply reflect the diversity within the non-trial population, emotional issues relating to a life changing treatment and the impact of the COVID-19 pandemic. In view of the clinical significance of discontinuing triple therapy, every effort should be made to continue treatment while resolving or minimising any side effects.

We report our experience of using sweat chloride and markers of clinical stability to titrate dose reductions of ELX/TEZ/IVA in individuals who experience mental health deterioration following commencement of triple therapy.

2. Methods

All adults who had been prescribed ELX/TEZ/IVA, were identified using the Leeds Adult CF Unit electronic patient records. This included individuals who had experienced adverse events (AEs) requiring dose adjustment or drug discontinuation. Type of AEs, and interval time between onset and start of treatment, were extracted. Suspected AEs were reported to the Medicines and Healthcare products Regulatory Agency (MHRA), in line with post-marketing surveillance. Individuals who received a previous solid organ trans-

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plant (kidney or liver) were excluded from analysis, as aetiology of AEs may relate to interaction between ELX/TEZ/IVA and tacrolimus. All subjects had attended a one-off dedicated CFTR modulator initiation clinic, during which a baseline sweat test (Macroduct® Sweat Collection System) was undertaken [7].

Individuals who presented with mental health problems were thoroughly assessed by senior CF clinicians and psychologists and each case was discussed as part of a CFTR modulator weekly multidisciplinary meeting so that a standardise approach was used across the unit.

An internal standardised protocol was followed to titrate dose adjustment using serial sweat chloride measurements (Supplementary file). The potential implications of reducing the dose of ELX/TEZ/IVA were discussed and agreed, with each individual, following an in-depth discussion. When dose titration was required, a repeated sweat chloride measurement was undertaken prior to the morning dose of ELX/TEZ/IVA and 2–4 weeks following dose adjustment. The interval time of at least two weeks was chosen based on clinical trial data showing that a maximal reduction in sweat chloride concentration occurs by day 15 and remains consistent throughout the follow-up [2,3].

Individuals were referred for psychological support, and, where appropriate, treated with anti-depressants. Interventions were tailored to individual needs and included cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT), compassion-focussed therapy (CFT), cognitive analytic therapy (CAT) and motivational interviewing (MI).

All patients had previously consented to their data being used for research purposes.

3. Results

Between October 2019 and October 2020, 266 adults, including both modulator-naïve and those who switched treatment from TEZ/IVA or IVA, started ELX/TEZ/IVA. Four were liver transplant recipients and excluded from this case series.

Thirty-three individuals (12.6%) experienced one or more clinically significant adverse events on ELX/TEZ/IVA. Out of these, 12 presented with rashes, which were self-limiting in most cases, but required temporary suspension of treatment in two young women. Three subjects had persistent derangement of liver function tests, with the need for liver biopsy for further assessment and temporary discontinuation of drug in one case.

Nineteen individuals reported deterioration in mental health with anxiety, low mood, insomnia and “brain fog” with reduced attention and concentration span, which impacted on day-to-day activity and quality of life. Twelve individuals (63.1%) had a past medical history of anxiety and/or low mood for which they had received regular psychology input.

Thirteen adults, of whom nine (69.2%) had previous history of mental health morbidity, underwent dose reduction of ELX/TEZ/IVA with monitoring of sweat test and lung function, whereas four preferred to stop treatment, and two decided to continue with full dose of treatment while starting psychological support.

Table 1 summarises the baseline characteristics of the 13 individuals who underwent dose reduction. Most (83.4%) were F508del homozygous and had received TEZ/IVA prior to starting treatment (6 female, age 20–48 years); 3 individuals had CF-related liver disease defined as fatty infiltration on ultrasound, and one had evidence of cirrhosis. The baseline sweat test was not available in two cases, due to insufficient sample despite several attempts, and/or COVID restrictions. Adverse events, dose adjustment and sweat chloride results are summarised in Table 2. All individuals were referred for psychological support and six (46.15%) were prescribed antidepressants, including the two adults who were on treatment prior to starting ELX/TEZ/IVA.

Table 1
Baseline characteristics of the population included in the case series.

	***N* = 13**
Median age [range], years	35 [18–48]
Female Sex, n (%)	10 (76.9%)
Genotype	
F508del/F508del	11 (84.6%)
F508del/MF	1 (7.7%)
F508del/RF	1 (7.7%)
CF-related diabetes	6 (50%)
CF-related liver disease	3 (25%)
CF-related cirrhosis	1 (8.3%)
Previous modulator	
TEZ/IVA	11 (84.6%)
IVA	1 (7.7%)
None	1 (7.7%)
Anxiety/depression	9 (69.2%)
Antidepressant	
History of use	4 (30.6%)
At start of ELX/TEZ/IVA	2 (15.3%)

Dose adjustment resulted in normal (<30 mmol l^{-1}) and borderline sweat chloride (30–60 mmol l^{-1}) levels in six (46.2%) and seven (53.2%) cases respectively. Lung function and respiratory symptoms were closely monitored in conjunction with sweat chloride, which remained above pre-triple therapy values in all individuals (Table 2). Further adjustment in the dose due to elevated sweat test and/or respiratory symptoms was required in three cases. A rapid resolution or improvement in mental health AEs occurred in 10/13 (77%) of cases. In the reaming three cases, symptoms only resolved after discontinuing treatment ($n = 2$) or in one case switched back to ivacaftor as a single agent (Table 2).

4. Discussion

In this case series, we report the use of sweat chloride as an indirect biomarker to guide dose adjustments of ELX/TEZ/IVA in people experiencing significant mental health problems (depression, anxiety, brain fog and insomnia) after starting treatment. The frequency of adverse events observed in our cohort, appears higher than levels previously reported in the CF population (13–33%) [8,9]. A strategy combining dose reduction and psychological support potentially avoids discontinuation of treatment, whilst reducing side effects.

We hypothesise that these AEs are a result of a combination of predisposition to anxiety and/or depression, the presence of a premorbid mental health condition, individual variation in elexacaftor metabolism and increased systemic CFTR expression.

Worsening anxiety and depression has been reported following initiation of lumacaftor/ivacaftor in adolescent females with CF [10]. Lumacaftor is known to induce CYP3A, and has the potential of reducing exposures of drugs that are CYP3A substrates such as ELX/TEZ/IVA and many antidepressants [5]. However, none of the individuals included in this series had been on lumacaftor immediately prior to starting triple therapy. Most of the subjects presented in this case series had been on dual combination therapy with TEZ/IVA prior to commencing triple therapy, suggesting that the development of new symptoms was most likely associated with ELX. This could be the result of the significant increase in CFTR function, or a possible serotoninergic effect of ELX [4]. Halving the ELX/TEZ/IVA dose in the morning proved effective in most cases. Unlike TEZ/IVA, the main metabolite of ELX has similar potency [11] and heterogeneity in metabolism has the potential of increasing or reducing drug levels. This might partially explain why sweat chloride concentration remained relatively stable despite halving the dose

Table 2
Adverse events, and response to dose reduction.

Case	Adverse event (and interval time)	Dose reduction	Response	Outcome	Sweat chloride (mmol L^{-1})			FEV1		
					Baseline	Standard dose	Adjusted dose	Baseline	Standard dose	Adjusted dose
1	Low mood, Anxiety, Insomnia (4 months)	ELX/TEZ/IVA x 1 morning	Minimal improvement in all AE symptoms	Stopped ELX/TEZ/IVA due to persistent symptoms	92	34	29	21%	52%	44%
2	Insomnia, Anxiety (1 month)	ELX/TEZ/IVA x1 morning + IVA night	Resolution of anxiety and insomnia	Continues on reduced dose	107	23	32	80%	83%	85%
3	Low mood, anxiety, Insomnia (4 months)	ELX/TEZ/IVA x1 morning + IVA night	Resolution of the AE symptoms, mild respiratory symptoms	Continues on reduced dose	90	54	61	58%	75%	73%
		Further dose adjustment: ELX/TEZ/IVA x1.5 morning + IVA night	Overall improvement				36			80%
4	Insomnia, low mood, Short-term memory loss (3 months)	ELX/TEZ/IVA x1 morning + IVA night	Improvement in most AE symptoms. Some persistence of short-term memory loss	Continues on reduced dose	n/a	48	41	50%	67%	66%
5	Stress, anxiety and increase in ALT (2 months)	ELX/TEZ/IVA x1 morning + IVA night	Minimal improvement in AE symptoms,	Stopped ELX/TEZ/IVA due to persistent symptoms	90	18	20	66%	78%	77%
		Further dose adjustment: ELX/TEZ/IVA x1 morning	No further improvement				23			73%
6	Insomnia, low mood, Anxiety (1 month)	ELX/TEZ/IVA x1 morning + IVA night	Improvement in AE symptoms, but increased cough	Continues on reduced dose	100	29	42	44%	53%	46%
		Further dose adjustment: ELX/TEZ/IVA x1.5 morning + IVA night	Resolution of AE and respiratory symptoms				36			49%

(*continued on next page*)

Table 2 (*continued*)

Case	Adverse event (and interval time)	Dose reduction	Response	Outcome	Sweat chloride (mmol L^{-1})			FEV1		
					Baseline	Standard dose	Adjusted dose	Baseline	Standard dose	Adjusted dose
7	Insomnia and sleep fragmentation (1 month)	ELX/TEZ/IVA x1 morning + IVA night	Resolution of AE symptoms	Continues on reduced dose	107	46	56	38%	45%	44%
8	Insomnia (1 month)	ELX/TEZ/IVA x1 morning	Improvement in AE symptoms, but increased cough	Continues on reduced dose	n/a	n/a	37	67%	78%	75%
		Further dose adjustment: ELX/TEZ/IVA 1 BD (Patient wished to avoid IVA pm)	Resolution of all symptom				17			78%
9	Anxiety, panic attacks (1 month)	ELX/TEZ/IVA x1 morning + IVA night	Improvement in all symptoms	Continues on reduced dose	99	20	49	83%	88%	80%
10	Anxiety, insomnia (1 month)	ELX/TEZ/IVA x1 morning + IVA night	Resolution of AE symptoms	Continues on reduce dose	64	20	20	58%	83%	80%
11	Anxiety, low mood, hallucination (3 months)	ELX/TEZ/IVA x1 morning + IVA night	Improvement in AE symptoms	Continues on reduced dose	95	32	30	46%	61%	58%
12	Anxiety, low mood (2 weeks)	ELX/TEZ/IVA x1 morning + IVA night	AE fully resolved when switched back to IVA	Switched back to IVA	39	11	11	60%	60%	59%
13	Anxiety, low mood, anger (6 months)	ELX/TEZ/IVA x1 morning + IVA night	Improvement in AE symptoms	Continues on reduced dose	104	14	23	66%	79%	77%

It was reassuring that dose adjustments, in conjunction with psychological support and psychoactive treatment as appropriate, led to an improvement or resolution in AE without short-term impact on clinical outcomes. Long term evaluation and monitoring is ongoing to ensure continued stability.

We present here a case series with data extracted from clinical notes and resulting from a structured clinical assessment. As such main limitations of this report include the lack of formal baseline and follow-up standardised assessment of mental health and of respiratory symptoms using validated questionnaire, and the lack of a comparison group.

In conclusion, the introduction of ELX/TEZ/IVA therapy has been life changing for many individuals with CF. In a minority of subjects, treatment can result in significant side effects with deterioration of mental health, which may be ameliorated by dose adjustment without significant clinical deterioration. Sweat chloride concentration can provide a practical and routinely available surrogate marker of CFTR function to clinically monitor and guide dose adjustment when and if required, as drug levels are currently not available in routine clinical practice. Further studies looking in a systematic way at the impact of currently available and future modulators on mental health, using standardized questionnaire, may help to further characterise the problem.

Contributors

Contributors DP and GS conceived this project. LG, KP undertook the sweat testing and supported clinical monitoring. DP, GS, NS, EW, CE, and IC are part of the CFTR MDT supporting dose adjustments. All authors were involved in interpreting the findings and revising drafts and agreeing the final version.

Declaration of Competing Interest

D Peckham reports past educational speaker and advisory board fees from Vertex. N Shaw reports speaker fees for educational talks from Vertex.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.05.001.

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