Central nervous system safety of long-acting cabotegravir/rilpivirine in patients with previous oral INSTI-related CNS toxicity

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Background: central nervous system (CNS) toxicity is the main reason for treatment withdrawal in patients receiving oral integrase inhibitors (INSTI), and there is not information on the role of long-acting (LA) cabotegravir/rilpivirine (C/R) in this setting.

Material and Methods: evaluation of the CNS safety of C/R in patients with prior intolerance to oral INSTI in a clinical cohort of 343 patients starting C/R between January 2023 and September 2024 at an HIV Outpatient clinic from a tertiary hospital in Madrid, Spain. C/R was administered baseline-w4 and each 8w thereafter, without oral leading.

Baseline Features (N=343)

Age (median, range) ≥ 50 (N,%)	43,5 (23-76) 126 (37)
Female (N,%)	44 (13)
Risk factor for HIV (N,%)	MSM 259 (75)
Prior ART (N, %) Median: 9y (0-34)	INSTI: 277 (81) NNRTI: 56 (16) PI: 10 (3)
Number of prior ART lines (median,range) ≥ 5 (N,%)	3 (1-21) 116 (34)
AIDS (N,%)	53 (15)
CD4 count (cells/µL; median, range)	711 (31-2089)
Undetectable HIV RNA (n,%)	338 (98)
BMI (median, range)	25 (15-43) 10% ≥30 (N=36)

HIV SUBTYPE (n,%) * Available in 126 (37%)	B (109, 86%) A (<2%)
Comorbidities (N,%) - Hypertension - Dyslipidemia - Psychiatric - Cancer	184 (54) 43 (12) 42 (12) 24(7) 10 (3)
Concomitant therapies (N,%)	155 (45)
Reason for change to C/R (%)	Medical proposal 52 Patient´s request 48
Prior NNRTI experience (N,%) -NNRTI mutations* (N ,%)	215 (63) 6 (1,7)
***Y181C (n=1) , K103N (n=3), N348+V108I (n=1), V106I (n=1)**	
HBsAb (N,%)	275 (80)
Isolated HBcAb (N,%)	19 (5,5)

C/R withdrawal (N=25)

Adverse Events (N,%)	17 (4,9)
Viral failure (N,%)	3 (0,8)
Other (N,%)	5 (1,5)

CNS symptoms	**N=9 (2,6)**
IRS effects	N=5 (1,2)
Allergic reaction	N=1 (0,3)
Malaise	N=2 (0,6)

Comparison of baseline and evolutive features between patients with and without prior INSTI-related CNS Toxicity

	Prior INSTI-related CNS Toxicity (n=31)	No Prior INSTI-related CNS Toxicity (n=312)	P
Female (N, %)	7 (23%)	37 (12%)	NS
Age (mean ± SD)	52±11	44±12	0.001*
BMI (mean ± SD)	24± 3	26±4	0.05
Years on ART (mean ± SD)	15±7	11± 8	0.005*
Lines of prior ART (mean ± SD)	7±4	4±4	0.002*
Prior AIDS (%)	23	15	NS
CD4 count (cells/µL, mean± SD)	762 ± 232	757 ± 329	NS
Comorbidities (%)	81	51	0.001*
INSTI-based ART just before C/R (%)	45%	84%	0.0001*
CNS toxicity on C/R (N,%)	7 (23)	5 (1,9)	0.0001*
C/R Withdrawal due to CNS toxicity (N,%)	5/31 (16%)	4/312 (1,3%)	0.0001*

Features and outcomes of patients with CNS toxicity leading to C/R withdrawal

	Gender	Age	ART prior to C/R	Prior oral INSTI related to CNS Toxicity *leading to withdrawal	Number of C/R Doses Prior to withdrawal	ART after C/R withdrawal	Resolution of CNS symptoms
P1	F	63	c/EVG/TAF/FTC	BIC	8	c/EVG/TAF/FTC	YES
P2	M	35	BIC/TAF/FTC	NO	2	DOR/3TC	YES
P3	M	61	DTG/3TC	DTG	7	DOR/3TC	YES
P4	F	53	DTG/3TC	NO	8	BIC/TAF/FTC	YES
P5	M	72	BIC/TAF/FTC	BIC, DTG	3	c/DRV/TAF/FTC	YES
P6	F	70	DTG/3TC	NO	4	DTG/3TC	YES
P7	M	63	BIC/TAF/FTC	NO	3	BIC/TAF/FTC	YES
P8	F	56	c/EVG/TAF/FTC	BIC	3	c/EVG/TAF/FTC	YES
P9	M	52	c/EVG/TAF/FTC	BIC	2	c/EVG/TAF/FTC	YES

Conclusions

In this cohort of heavily pretreated patients, the rate of CNS-related toxicity withdrawal was low (2.6%), but the incidence of CNS toxicity and CNS-related withdrawals were significantly higher in patients with prior oral INSTI-related CNS adverse events