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CROI
Conference on Retroviruses and Opportunistic Infections

WASHINGTON STATE CONVENTION CENTER
Seattle, Washington
March 4–7, 2019

BICTEGRAVIR CONCENTRATIONS AND VIRAL SUPPRESSION IN CSF of HIV–INFECTED PATIENTS

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Background

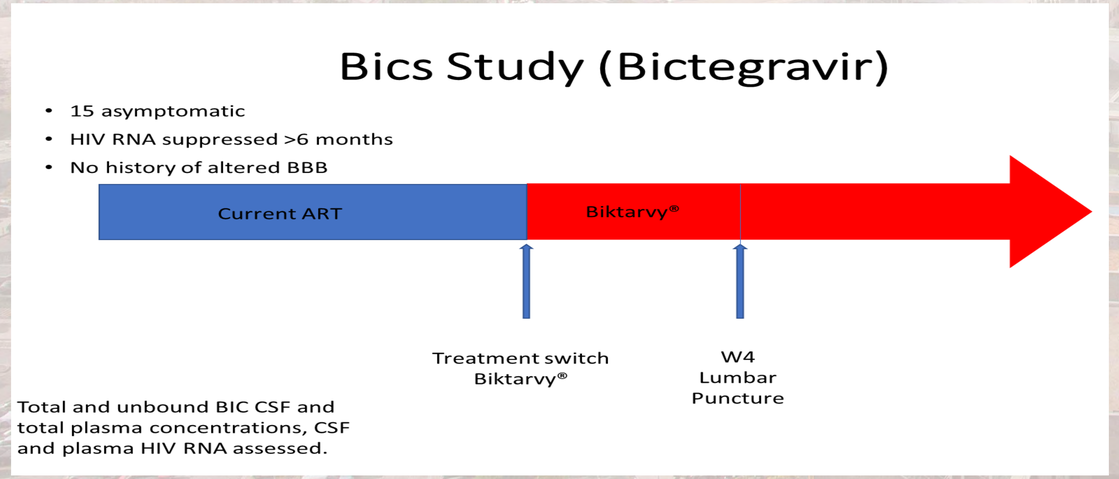
Bictegravir (BIC) is a novel, potent, integrase inhibitor combined in a fix-dose pill with tenofovir alafenamide (TAF) and emtricitabine (FTC). BIC differs from previously known structures in that it contains a unique bridged bicyclic ring and a distinct benzyl tail consisting of a tri substituted 2,4,6-trifluorobenzyl moiety. These changes resulted in increased plasma protein binding (>99%) to improve its solubility. These two physicochemical characteristics are crucial determinants of drug penetration into the CNS. The assessment of the antiviral activity of new drugs in compartments such as CSF is relevant to avoid HIV-related neurocognitive disorders. In addition, the role of unbound ARV drug concentrations has been scarcely evaluated.

Objective

The aim of our study was to determine total and unbound BIC levels in cerebrospinal fluid (CSF) as well as HIV viral load in this compartment.

Methods

This is a single-arm, open-label, single-center study. After an initial assessment, 15 participants switched from stable ART to FTC/TAF/BIC (Biktarvy®). At week 4, total plasma and total and unbound CSF concentrations of BIC were measured 24 hs post-dose, using a validated LC-MS methodology (assay calibration range is 10-10,000 ng/ml for plasma and 1-100 ng/ml for CSF). HIV RNA was measured in plasma and CSF by RT-PCR (LLQ 40 copies/mL).



Total and unbound BIC CSF and total plasma concentrations, CSF and plasma HIV RNA assessed.

Results

Baseline Characteristcs

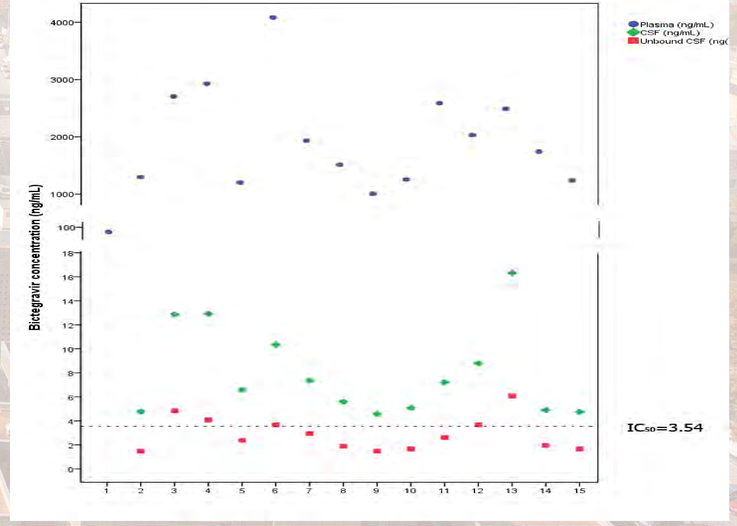
Variable	N	Median (IQR)
Age (years)	15	42 (37 - 56)
BMI	15	24.7 (23.25-29.85)
Baseline CD4	15	315 (80 – 476)
Baseline Viral load: copies/ml	15	60000 (30094 – 410304.5)
Hemoglobin (g/L)	15	154 (145 – 158)
WBC	15	6,1 (5,3 – 8.1)
CD4 cells (cells/ml)	15	801 (628 – 1011)
CD4 (%)	15	35 (30 – 42)
CSF Results		
Cells	15	<0.001 x10E9/L
Glucose (mmol/L)	15	3,5 (3 - 3,7)
Proteins (g/L)	15	0,33 (0,26 - 0,43)

CSF and plasma results

ID	HIV RNA CSF copies/ml	HIV RNA Plasma copies/ml	Bictegravir plasma ng/ml	Bictegravir CSF ng/ml	Unbound CSF Bictegravir ng/ml	BIC ratio CSF/plasma
*1	<40	<40	97.9	<LLQ	<LLQ	n/a
2	<40	<40	1297.3	4.7	1,4	0.003
3	<40	<40	2702.2	12.8	4,8	0.004
4	<40	<40	2925.05	12.9	4,07	0.004
5	<40	<40	1199.9	6.5	2,3	0.005
6	<40	<40	4082.08	10.3	3,6	0.002
7	<40	<40	1932.5	7.3	2,9	0.003
8	<40	<40	1512.4	5.5	1,8	0.003
9	<40	<40	1003.9	4.5	1,4	0.004
10	<40	<40	1254.7	5.08	1,6	0.004
11	<40	<40	2586.7	7.2	2,6	0.002
12	<40	<40	2030.6	8.7	3,6	0.004
13	<40	<40	2488.2	16.3	6,06	0.006
14	<40	<40	1741.8	4.8	1,9	0.002
15	<40	<40	1237.2	4.7	1,6	0.003
Median (range)	<40	<40	1837.1 (1250.4 – 2615.6)	6.9 (4.8 – 10.9)	2.48 (1.4-6.06)	0.003 (0.003 – 0.004)

*Pt concomitantly taking self-prescribed magnesium supplements.

A total of 15 plasma an 15 CSF samples were collected. At baseline, median CD4 count was 801cells/uL (628-1011), HIV viral load was <40 copies/ml in all subjects. Most patients switched from Genvoya® and Triumeq® (57,2%). One patient presented with unexpected low BIC concentrations in plasma and CSF while concomitantly taking self-prescribed magnesium supplements. Around 30% of total CSF BIC was unbound. These concentrations were lower than expected if we assume that most of the drug in CSF should be "free" (then active), as the CSF is a fluid with low protein content.



Conclusions

Although the target concentrations are unknown, total trough BIC concentrations in CSF were above the in vitro 50% inhibitory concentration for wild-type HIV (IC50: 3.54 ng/mL). On the other hand, BIC unbound concentrations were below the IC50 threshold in many pts, suggesting that BIC exposure to the CNS might not be optimal. However all subjects presented with CSF viral suppression thus, given in combination with FTC/TAF, BIC may contribute to inhibit viral replication in this compartment. More data about the clinical significance of unbound concentrations of ARV drugs in compartments such as CSF are needed.

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