Abstract #426

EFFECT OF DOLUTEGRAVIR PLASMA CONCENTRATION ON CENTRAL NERVOUS SYSTEM SIDE EFFECTS

Hiroki Yagura[1], Dai Watanabe[2], Takao Nakauchi[1], Kosuke Tomishima[1], Daisuke Kasai[2], Yasuharu Nishida[2], Munehiro Yoshino[3], Tomoko Uehira[2], Kunio Yamazaki[1], Takuma Shirasaka[2]
[1]Department of Pharmacy, National Hospital Organization Osaka National Hospital [2]AIDS Medical Center, National Hospital Organization Osaka National Hospital
[3]Department of Pharmacy, National Hospital Organization Osaka-minami Medical Center

CROI 2017 seattle

Background

Dolutegravir (DTG), a second-generation HIV integrase inhibitor that is easily administered once daily, was shown to offer non-inferior efficacy in comparison with other medications in phase III trials[1)]. At present, DTG is increasingly being prescribed, particularly in developed countries, including Japan, and has previously been reported to induce side effects in the central nervous system (CNS), such as insomnia and headache[2)]. However, the mechanisms of action including associations between DTG plasma concentration and CNS side effects remain unclear.

Objective

We examined the association between DTG plasma trough concentration and CNS side effects(CNSSEs), in Japanese HIV-1-infected patients.

Patients & Methods

Patients

We recruited 162 HIV-infected patients who had undergone anti-retroviral treatment, including DTG treatment, at Osaka National Hospital, Japan, between April 2014 and March 2016. DTG plasma trough concentration was measured, and the association between DTG concentration and CNS side effects was statistically analyzed within 6 months of DTG introduction. This study was reviewed and approved by the institutional review board of the National Hospital Organization Osaka National Hospital (approval number: 0838).

DTG plasma trough concentrations

Blood samples were collected at 20-28 h after oral administration of DTG under repetitive administration for ≥10 days. Samples were centrifuged at 3000 rpm for 10 min to separate 2 mL of plasma. Plasma was then stored at -80°C until required for analysis. Plasma DTG concentration was measured by liquid chromatography-mass spectrometry[3)].

Results

Table 1. Demographics of participants

	Total	Without CNNSEs	With CNSSEs	*p*
Participants (n, %)	162	121 (75%)	41 (25%)	
Age (years), median [IQR]	43 [38–52]	43 [38–52]	42 [36–48]	0.1754
Males (n, %)	154(95%)	115 (95%)	39(95%)	0.6918
Body weight (kg), median [IQR]	65[59–73]	65 [59–73]	65[58–73]	0.6126
Treatment-naïve (n, %)	36 (22%)	23 (19%)	13 (32%)	0.1407
Medical examination history of psychiatry (n, %)	19 (12%)	15 (12%)	4 (10%)	0.8624
Taking at bedtime (n, %)	12 (7%)	10 (8%)	2 (5%)	0.9778
CD4 cell count (cells/μL), median [IQR]	488 [344–615]	482 [342–615]	501 [347–571]	0.8133
Participants with HIV-1-RNA level <50 at time of sampling (n, %)	158 (98%)	115 (95%)	39 (95%)	0.6918
Use of antiretroviral agents (n, %)				
Tenofovir	80 (49%)	55 (45%)	25 (61%)	0.1242
Abacavir	72 (45%)	59 (49%)	13 (32%)	0.0859
Protease inhibitor	5 (3%)	4 (3%)	1 (2%)	0.8064
NNRTI	5 (3%)	3 (3%)	2 (5%)	0.8064
Duration of DTG treatment (days), median [IQR]	92 [58–175]	95 [62–180]	88 [56–165]	0.6972
HBV infection (n, %)	9 (6%)	7 (6%)	2 (5%)	0.8608
HCV infection (n, %)	2 (1%)	2 (2%)	0 (0%)	0.9919

NNRTI, non-nucleoside reverse transcriptase inhibitor; IQR, interquartile range

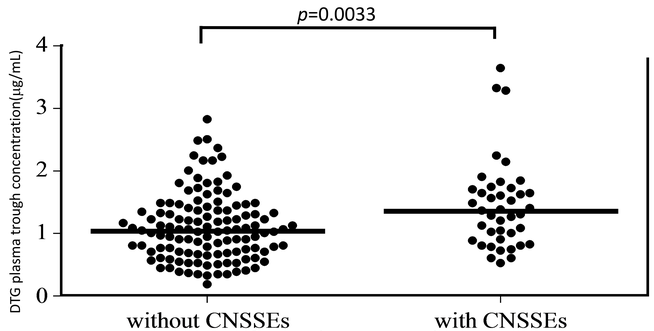

Figure 1. Comparison of DTG plasma-trough concentration between patients with and without CNSSEs. Horizontal straight line indicates median value.

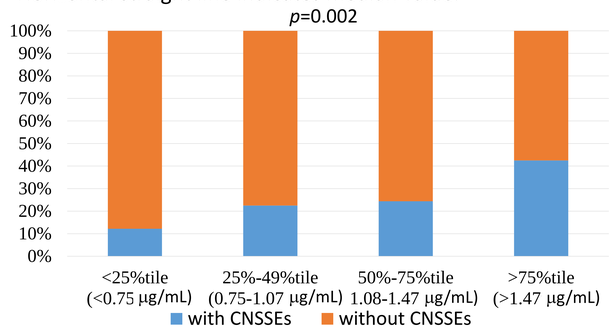

Figure 2;Association between DTG plasma-trough concentration and CNSSEs rate.

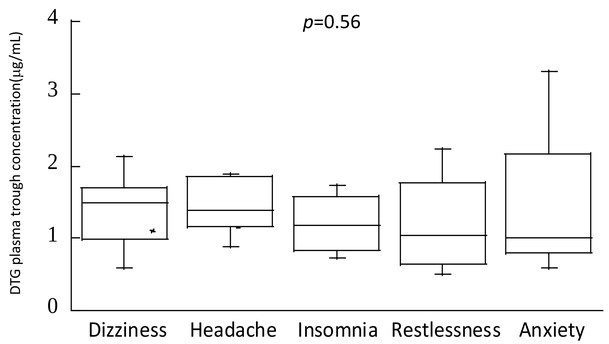

Figure 3. Comparison of DTG plasma-trough concentrations according to symptoms of CNSSEs.

- ✓ At least one CNS side effect was observed in 41 patients (25%), including dizziness (14/41, 34%), headache (11/41, 27%), insomnia (11/41, 27%), restlessness (4/41, 10%), and anxiety (3/41, 7%).
- ✓ Patients with CNS side effects showed higher trough DTG plasma concentrations compared with subjects without symptoms (median, 1.34 μg/ml vs 1.03 μg/ml, p=0.003 by univariate Mann-Whitney U-test). A positive correlation was observed between DTG concentration and frequency of CNS side effects (p=0.002 by Cochran-Armitage test).
- ✓ No significant difference in DTG concentration was observed among CNS symptoms (p=0.56 by Kruskal-Wallis test).

Conclusions

In this study, a positive correlation between DTG plasma trough concentration and CNS side effects was identified in a Japanese population. This implies the importance of measuring DTG concentration for evaluating CNS side effects.

Limitations

This study was performed at a single institution with a limited number of Japanese patients.

Acknowledgments

We are grateful to all the study participants. This work was supported by the Research Program on HIV/AIDS from the Japan Agency for Medical Research and Development, AMED to K.Y.

References

1) Raffi F, et al. Lancet Infect Dis, 2013;11:927-35.
2) Van den Berk G, et al. Conference on Retroviruses and Opportunistic Infections (CROI), 2016, Abstract 948.
3) Takahashi M, et al. The 28th Annual Meeting of the Japanese Society for AIDS Research, 2014, P-025

National Hospital Organization Osaka National Hospital, Japan