*UGT1A1*6* Polymorphisms are Predictive of High Plasma Concentrations of Dolutegravir in Japanese Individuals

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Introduction

Dolutegravir (DTG), an HIV integrase inhibitor, is metabolized mainly by glucuronidation via UDP-glucuronosyltransferase 1A1 (UGT1A1) (Fig. 1).
Several UGT1A1 polymorphisms have been correlated with the UGT1A1 expression level and enzymatic activity. Allele frequencies of UGT1A1*28 vary with race, and are relatively high in Caucasian and African-American Populations[1)]. Allele frequencies of UGT1A1*6 also vary with race, and are low in Western populations, but high in Asian populations[2)].

We compared the effects of the two polymorphic alleles, UGT1A1*6 and UGT1A1*28, on plasma DTG concentrations in Japanese HIV-1-infected patients.

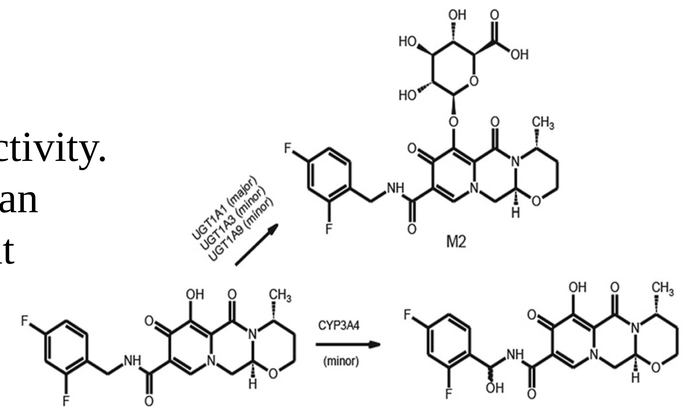

Fig. 1 Metabolic scheme of dolutegravir[3)]

Materials & Methods

The trough concentrations of plasma DTG were measured in 69 Japanese HIV-1 patients who were taking DTG at Osaka National Hospital, and UGT1A1 genetic screening (*6 and *28) was performed. UGT1A1 was genotyped using the sequencing method[4)]. Plasma was sampled immediately before DTG administration, and plasma DTG concentrations were determined using liquid chromatography-mass spectrometry[5)]. This study was reviewed and approved by the Institutional Review Board of the National Hospital Organization Osaka National Hospital (approval number: 0838).

Demographics and genotypes of participants

Genotype	−/−	−/*28	−/*6	*28/*28	*6/*28	*6/*6	p value
Participants (n, %)	32 (47%)	10 (14%)	15 (22%)	3 (4%)	2 (3%)	7 (10%)	
Age (years)	46 [41–49]	49 [42–56]	43 [40 –46]	42 [41–43]	53 [47–59]	44 [38–50]	0.5635
Males (n, %)	29 (94%)	9 (90%)	14 (93%)	3 (100%)	2 (100%)	7 (100%)	0.9376
Body weight (kg)	66 [62–75]	67 [60–71]	71 [63–82]	64 [61–77]	55 [53–56]	68 [63–73]	0.3431
CD4 cell count (cells/μL)	453 [293–575]	437 [366–570]	378 [321–550]	434 [406–667]	386 [366–405]	578 [532–648]	0.5987
Participants with undetectable HIV-1 RNA levels (n, %)	29 (94%)	10 (100%)	12 (80%)	3 (100%)	2 (100%)	6 (86%)	0.6317
Use of antiretroviral agents (n, %)							
Tenofovir	16 (50%)	5 (50%)	10 (67%)	2 (67%)	2 (100%)	4 (57%)	0.7561
Abacavir	16 (50%)	5 (40%)	5 (33%)	1 (33%)	0 (0%)	2 (29%)	0.8341
Protease inhibitor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0000
NNRTI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0.1221
Duration of DTG treatment (days)	84 [35–116]	91 [63–127]	71 [31–84]	67 [62–111]	43 [41–44]	77 [30–94]	0.8418
HBV infection (n, %)	3 (10%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0.8011
HCV infection (n, %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000

IQR: interquartile range; NNRTI: non-nucleoside reverse transcriptase inhibitor; Values represent medians [IQR]

Results

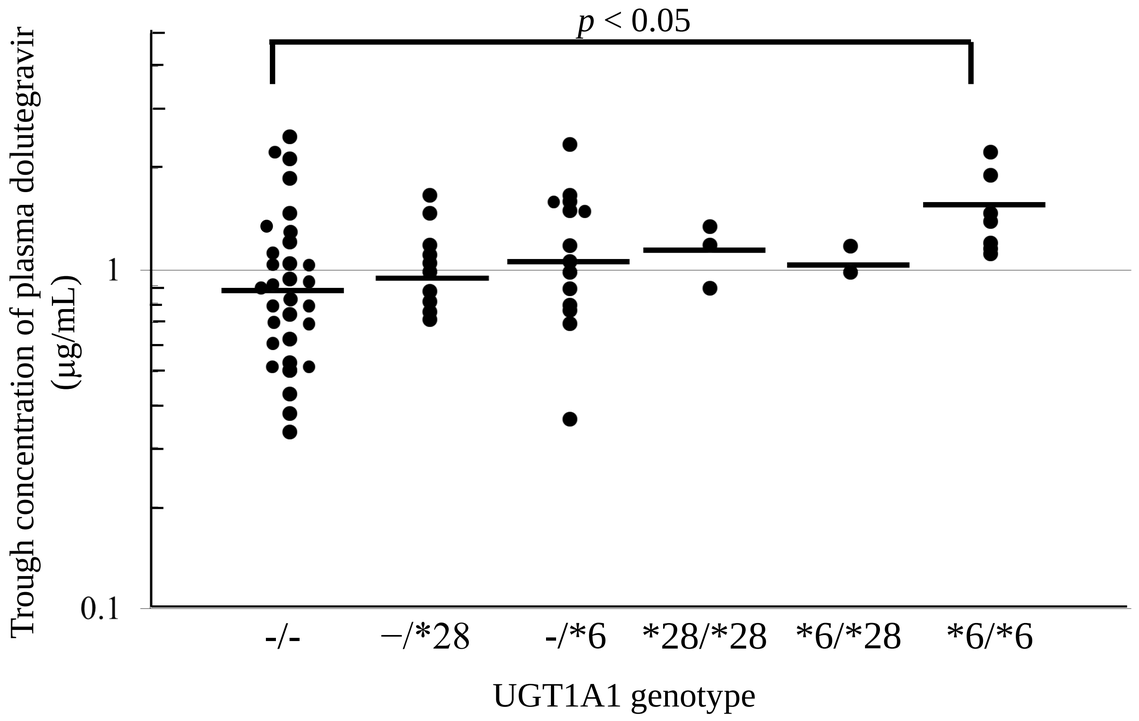

Fig. 2 Correlation between UGT1A1 polymorphisms and the trough concentration of plasma dolutegravir. The horizontal straight lines indicate the median values.

- The frequencies of UGT1A1*6 and UGT1A1*28 were 23% and 13%, respectively.
- The trough concentrations of plasma DTG were significantly higher in patients homozygous for UGT1A1*6 (n = 7, median: 1.4 μg/mL) than in patients carrying the normal allele (n = 32, median: 0.89 μg/mL; p = 0.011).
- The trough concentrations of plasma DTG in patients homozygous for UGT1A1*28 (n = 3, median: 1.2 μg/mL), compound heterozygous for UGT1A1*6 and UGT1A1*28 (n = 2, 0.98 and 1.2 μg/mL, respectively), or heterozygous for UGT1A1*6 and UGT1A1*28 (n = 15 and 10, median: 1.1 and 1.0 μg/mL, respectively) were not significantly different from those in patients homozygous for the normal allele.

Conclusions

The trough concentrations of plasma DTG were significantly higher in patients homozygous for UGT1A1*6 than in those with the normal allele. This suggests that the presence of UGT1A1*6 influences plasma DTG concentrations.

References

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