# Dolutegravir discontinuation due to neuropsychiatric adverse events: a pharmacogenetic case-control study

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Background

Dolutegravir (DTG) is a second-generation integrase strand transfer inhibitor recommended in first line antiretroviral regimens against HIV. Neuropsychaitric adverse events (NPAEs) represent a significant toxicity that may lead to drug discontinuation. This study aims to evaluate the association between DTG discontinuation due to NPAE and selected polymorphisms in pharmacogenes encoding proteins involved in transport and metabolism of DTG.

Methods

In this single-centre case-control study, cases were defined as patients who discontinued DTG due to NPAE, and controls as consecutively recruited patients with ongoing well-tolerated DTG treatment. Cases were identified through systematic review of the local HIV reference centre database. Symptoms leading to DTG discontinuation were determined by reviewing medical files. Pharmacogenomic panel testing was performed by next-generation sequencing for all included patients. The frequency of participants metabolism phenotype for *UGT1A1* (defined as poor, intermediate or normal metabolizer) and *CYP3A5* (defined as expresser or non-expresser), as well as genotypes for selected pharmacogene polymorphisms (*CYP3A4*22*, *ABCB1* c.3435T>C, *ABCG2* c.421C>A, *NR1I2* c.-22.-7659C>T, *POR*28*) were compared among cases and controls. Multivariable analysis was performed using logistic regression to identify potential risk factors for DTG discontinuation due to NPAE.

Results

36 cases and 98 controls were recruited. The most frequent complaints leading to DTG interruption were insomnia (61%), nightmares (19%) and irritability (19%). Cases and controls were comparable for main demographic parameters. The c.-22.-7659C>T (rs2472677) single nucleotide polymorphism (SNP) in *NR1I2*, the gene coding for pregnane X receptor (PXR), was found to be significantly and independently associated with a reduced risk of DTG discontinuation due to NPAE (odds ratio 0.36; 95% confidence interval: 0.15-0.88; P-value 0.02), displaying a dominant allele effect. Other studied polymorphisms, including polymorphisms of *UGT1A1*, showed no effect.

Conclusions

We found *NR1I2* c.-22.-7659C>T to be independently associated with a reduced risk of DTG discontinuation due to NPAE. Further studies should assess the impact of this SNP on the pharmacokinetics and pharmacodynamics of DTG, as PXR is a key regulator of DTG phase I/II metabolism and transport.

Key Words

Dolutegravir, toxicity, neuropsychiatric toxicity, pharmacogenetics, pregnane X receptor, NR1I2