The Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Individuals Receiving Integrase Strand Transfer Inhibitors: Results from the EuroSIDA Study

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BACKGROUND

Hypersensitivity reaction (HSR) and hepatotoxicity are rare but potentially serious side effects of antiretroviral use. This post-authorisation safety study aimed to establish the incidence of discontinuations due to HSR, hepatotoxicity or severe skin rash among users of abacavir (ABC) or elvitegravir (EVG) in a real-world setting.

METHODS

HIV-positive individuals in EuroSIDA aged ≥18 years who started a combination antiretroviral therapy (cART) regimen containing DTG, RAL or EVG between 16/01/2014 and 23/01/2019 were analysed in four groups: DTG abacavir (ABC) and RAL or EVG ± ABC. All discontinuations were reviewed, and any suspected HSR, hepatotoxicity or severe skin rash events were adjudicated by an independent review committee. The incidence of discontinuations within each group was calculated.

RESULTS

- In total, 4366 individuals started at least one cART regimen including DTG, RAL or EVG with or without ABC (Table 1).
- Individuals started altogether 5116 integrase strand transfer inhibitor (INSTI)-containing cART regimens, containing 9180 person-years of follow-up (PYFU), with median follow-up 1.6 (interquartile range, IQR 0.7-2.8) years per treatment episode. Of the treatment episodes, 3074 (60.1%) were with DTG and 2042 (39.9%) were with RAL or EVG.
- There were 649 discontinuations in 5649 PYFU of DTG-containing regimens and 612 in 3531 PYFU of RAL- or EVG-containing regimens. The discontinuation rate for any reason for DTG was 115 (95% CI 106-124)/1000 PYFU and for RAL or EVG was 173 (CI 160-188)/1000 PYFU.
- After independent review, there were five HSR discontinuations, two for DTG (discontinuation rate 0.35, 95% CI 0.04-1.28/1000 PYFU), and three for RAL or EVG (0.85, CI 0.18-2.48/1000 PYFU). There was one hepatotoxicity discontinuation on DTG (ABC, 0.18, CI 0.09-0.19/1000 PYFU), and no severe skin rash discontinuation (Table 2 and Figure 2).
- Among those who discontinued, the most common reasons for discontinuing an INSTI-containing regimen were toxicity and physician’s decision (Figure 2).
- After adjustment, the rate of discontinuation of RAL- or EVG-containing regimens was >50% higher than for DTG regimens (aIRR 1.56, 95% CI 1.38-1.77, p < 0.0001). Apart from toxicity, the rate of discontinuations for all reported reasons was significantly higher among those on RAL or EVG (Figure 3).

DISCUSSION AND CONCLUSIONS

- During this five-year post-authorisation study in a real-world observational cohort, individuals contributed >8,000 PYFU on INSTI-containing cART regimens.
- Around 25% of INSTI regimens were discontinued, with discontinuation rates significantly higher among those on RAL- or EVG-containing regimens compared to DTG.
- In this real-world setting, discontinuations due to HSR or hepatotoxicity in INSTI users were very rare.
- After independent review, there were five HSR and one hepatotoxicity events, equivalent to one severe adverse event in approximately 1,500 person-years of INSTI use; the low number of severe events precluded detailed analyses.
- As this is an observational study, treatment decisions are made by the treating physician and confounding by indication cannot be excluded.

Table 1. Characteristics of INSTI users at baseline

Table 2. Discontinuations of INSTI regimens

Figure 1. Discontinuation rates for serious adverse events

Figure 2. Discontinuation reasons by treatment group

Figure 3. Adjusted discontinuation incidence rate ratios (IRRs) comparing discontinuations of RAL- or EVG-containing regimens with DTG discontinuations (reference)

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