Open Forum Infectious Diseases

CORRESPONDENCE

Is Dolutegravir Plus Atazanavir Overburdened With Concentration-Related Neurological Events Compared With Other Dual Regimens?

Dear Editor,

After the licensing of dolutegravir, a debate has begun to assess its tolerability beyond the pivotal trials' data comparing it with the tolerability profiles of the other integrase inhibitors on the market, with conflicting evidence [1, 2].

Boosted and unboosted atazanavir increase dolutegravir plasma concentrations by 1.5- to 2-fold [3].

In this study, we wanted to analyze whether a combination that yields high concentrations of dolutegravir may also cause more frequent or more severe adverse events.

This study is part of a comprehensive retrospective–prospective analysis of all subjects who have taken dolutegravir (even once in their life). The current analysis was performed on the population followed by the outpatient clinic of the 1st Division of Infectious Diseases of Luigi Sacco Hospital, Milan, and by that of the Institute of Clinical Infectious Diseases, Fondazione Policlinico Universitario Agostino Gemelli IRCCS–Catholic University of the Sacred Heart, Rome. Ethics committee approval has been obtained and informed consent signed within the larger "Odoacre" Observational Cohort to which the study subgroups pertain.

No further conditions were required to be eligible for the analysis. For this particular analysis only, dual therapies with dolutegravir were selected.

All subjects taking dolutegravir-based dual therapies for more than 1 day from January 2014 to June 2017 were retrospectively reviewed and prospectively assessed. Demographic data, treatment history, and virologic, immunologic, and clinical outcomes including adverse events were recorded at the time of the visits. In the case of adverse events, further questions were posed to the physicians. Adverse events and neurological adverse events were classified according to the the Common Terminology Criteria for Adverse Events (version 4.03) [4].

Five hundred seventy-three patients (10% of the HIV-infected outpatient population) were taking dolutegravir-based dual therapies.

Dolutegravir and its companion drug plasma C_{min} have been evaluated in 46 subjects on atazanavir (ATV; median [range], 2822 [187–6432] ng/mL), 35 on boosted darunavir (median [range], 1026 [191–4978] ng/mL), 31 on rilpivirine (median [range], 798 [194–3941] ng/mL), and 27 on lamivudine (median [range], 893 [198–2651] ng/mL), confirming the boosting effect of ATV.

The incidence rates of neurological adverse events and of discontinuations due to neurological adverse events are reported in Table 1. The overall incidence of neurological adverse events was very low (2.39%), and the incidence of those leading to discontinuation was only 1.95%, whereas the incidence of sleep disorders was 0.71%, as most patients were taking antiretrovirals

Table 1. Neurological AEs Leading or Not to Discontinuation According to the Different Regimens

	ATV + DTG	3TC + DTG	RPV + DTG	bDRV + DTG
	(n = 82)	(n = 213)	(n = 145)	(n = 103)
	(214 Patient-Years)	(575 Patient-Years)	(406 Patient-Years)	(294 Patient-Years)
Neurological AEs, No. (%)	2 (2.44)[a]	7 (3.29)[b]	3 (2.07)[c]	1 (0.97)[d]
Discontinued for neurological AEs, No. (%)	1 (1.22)[e]	6 (2.82)[f]	3 (2.07)[g]	1 (0.97)[h]
OR for neurological AEs [95% CI], *P*	0.34 [0.03–3.86] .39	0.19 [0.02–1.60] .13	0.46 [0.05–4.53] .51	
OR for discontinuing due to neurological AEs [95% CI], *P*[i]	0.70 [0.04–11.31] .80	0.23 [0.03–1.92] .17	0.46 [0.05–4.53] .51	

Abbreviations: 3TC, lamivudine; AEs, adverse events; ATV, boosted and unboosted atazanavir; bDRV, boosted darunavir; CI, confidence interval; DTG, dolutegravir; OR, odds ratio; RPV, rilpivirine.

[a]One fatigue, 1 headache and dizziness.

[b]Two insomnia, 1 nightmares, 1 headache, 1 headache + depression, 1 depression, 1 hallucinations.

[c]One headache, 1 headache and insomnia, 1 headache and dizziness.

[d]One headache and dizziness.

[e]One fatigue.

[f]All but 1 headache.

[g]One headache, 1 headache and insomnia, 1 headache and dizziness.

[h]One headache and dizziness.

[i]Compared with the best performer, bDRV + DTG.

in the morning. This is consistent with our previous report that morning dosing of dolutegravir-based regimens dramatically reduces sleep abnormalities [5]. No treatment group showed significantly different incidence in any of the categories.

In conclusion, in this population, the boosting effect exerted by atazanavir on dolutegravir does not seem to cause more neurological adverse events as compared with other dual therapy regimens.

Our observation confirms findings similar to those of Hoffmann et al. [6], who showed that neurological adverse events during dolutegravir-based regimens do not appear to be concentration-dependent.

However, Yagura et al. reported a significant correlation between dolutegravir plasma concentrations and central nervous system side effects in a Japanese population on a much different backbone (49% tenofovir/emtricitabine, 45% abacavir/lamivudine) [7].

A possible hypothesis may be that, as suggested initially by Hoffmann et al. [1], the backbone may also play a role in favoring the onset of neurological adverse events.

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