Short communication

Increased dose of dolutegravir as a potential rescue therapy in multi-experienced patients

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Background: The pilot Phase IIb VIKING study suggested that dolutegravir (DTG), an HIV integrase inhibitor (INI), is efficacious in INI-resistant patients at the 50 mg twice-daily dose. However, DTG response was most reduced in subjects carrying resistance-associated mutations at position G140 and Q148. These mutations can cause a 10–20-fold reduced susceptibility to DTG as well as a 96% lower odds of achieving HIV-1 RNA <50 copies/ml at week 24 if compared with those with no mutations at these positions.

Methods: Five multi-experienced patients harbouring the mutation complex G140–Q148, resistant to at least three drug classes, and previously exposed to DTG 50 mg twice daily, were treated with an increased dose of DTG (100 mg twice daily) in association with an optimized background regimen (OBR) based on their individual viral genotyping assays. The blood concentration of DTG was measured in order to determine whether a solubility issue is related with this high dosage.

Results: Four out of five patients attained an HIV-1 RNA <50 copies/ml at week 48 and no relevant adverse events were detected. The measured DTG blood concentration was that expected for the administered dosage, ruling out any solubility concerns.

Conclusions: For the first time 100 mg twice daily of DTG was administered to five multi-experienced patients harbouring the mutation complex G140–Q148. Although a small number of patients were tested, the results show a potential for a high-dose regimen of DTG as a rescue therapy in patients harbouring integrase strand transfer inhibitor resistant viruses.
harbouring Q148 + ≥2 mutations have 96% lower odds of achieving HIV-1 RNA <50 copies/ml at week 24 if compared with those with no Q148 mutations [6].

In this paper we present a study based on five multi-experienced patients, harbouring the mutation complex G140-Q148, resistant to at least three drug classes, three of which were previously exposed to DTG 50 mg twice daily. In order to overcome the resistance associated with the mutations, the five patients were treated with a higher dose of DTG (100 mg twice daily) associated with an optimized background regimen (OBR) based on their individual viral genotyping assays.

Methods

During the 6 weeks preceding the DTG 100 mg twice daily treatment, resistance tests for reverse transcriptase (RT), protease (PRO), gp41 and integrase (IN) were performed together with the determination of viral tropism. HIV-1 RNA was extracted from patient’s plasma samples using QIAamp viral RNA kit (Qiagen, Valencia, CA, USA) and sequences for RT, PRO and IN were obtained as described elsewhere [9,10].

Genotypic susceptibility scores (GSS) were calculated according to the Stanford HIVdb interpretation of genotypes and 2017 International AIDS society mutation list (gp 41 sequences) whereas co-receptor tropism was assessed by using the Trofile Coreceptor Tropism Assay (Monogram Biosciences, San Francisco, CA, USA).

CD4+ T-cell count was determined by flow cytometry and HIV-1 RNA was quantified by the Abbot Real-Time PCR (Abbott Molecular, Des Plaines, IL, USA).

The patient’s DTG, atazanavir and darunavir plasma concentrations were measured by a sensitive liquid chromatography tandem mass spectrometry (LC-MS/MS) using a coupled Qtrap 5500 mass spectrometer (AB Sciei, Framingham, MA, USA). Samples were liquid-liquid extracted using a commercial kit as described elsewhere [11]. The method was validated ‘in-house’ following the European Medicines Agency (EMA) guidelines [12].

Results

Five multi-experienced patients, four males and one female with age ranging between 32 and 52 years old (Table 1), were enrolled in this study. Three of them previously experienced a treatment involving DTG 50 mg twice daily with no success (Table 1). During the 6 weeks preceding the DTG 100 mg twice daily treatment, the patients were tested for resistance to nucleoside and non-nucleoside reverse transcriptase inhibitors, protease inhibitors and INSTIs. The corresponding viral genes were sequenced to find point mutations (data not shown). Based on their individual viral genotyping assays and coreceptor tropism data (Table 1) we estimated the genotypic and susceptibility score (GSS) and developed an OBR (Table 1). Both the HIV-1 RNA copies/ml and CD4+ T-cell count, at baseline, were measured and are reported in Table 1.

In the VIKING study the 100 mg dose of DTG was given as 50 mg twice daily because clinical pharmacology data indicated a solubility limit [5]. Because a DTG dose of 50 mg 4× a day would have been unsuitable for our study and could have caused a lack of adherence in our five domiciliary patients, we chose a twice daily formulation similar to the VIKING study: DTG 100 mg twice daily, every 12 h. To determine whether the drug solubility would have been an issue, the concentration of DTG in the patient’s blood was measured and compared with that of five patients treated with the standard dose of 50 mg DTG once per day. Approximately 12 h after the administration of the last DTG dose the patients’ blood was collected and the plasma drug concentration was measured by LC-MS/MS (Table 1).

The five patients treated with the standard 50 mg dose of DTG had an average plasma concentration, 12 h after drug administration, of 3,233 ±875 ng/ml, in agreement with available pharmacokinetic studies [13], whereas the five patients treated with DTG 100 mg twice daily had an average plasma concentration, 12 h after drug administration, of 12,851 ±4,756 ng/ml (Table 1). The fourfold difference in concentration between the two groups reveals that solubility does not seem to be an issue when 100 mg of DTG are administered as a single dose. Only one patient (number four) shows a low DTG concentration which might arise from an unreported lack of adherence (Table 1).

We also determined, in three patients, the concentration level of atazanavir (patient 2 and 3) and darunavir (patient 5), for which the standard doses were used. The concentration levels (data not shown) were in agreement with available pharmacokinetic studies [14] excluding major interactions with the 100 mg twice daily DTG dose.

The safety profile of DTG 100 mg/twice daily in the five patients group was similar to what observed in the VIKING studies [5,6] with no AE of grade >3 reported and specifically, despite the high dose of DTG used, no drug-related AEs and no neuropsychiatric events were observed.

During the treatment with DTG 100 mg twice daily and the associated OBR, four out of five patients attained an HIV-1 RNA <50 copies/ml at week 48 (Table 1) and their CD4+ T-cell count shows a large increase in three of the four patients (Table 1).

One patient did not respond to the treatment and his HIV-1 RNA remained detectable during the entire period of therapy (approximately 60 weeks; Table 1). It must be noted that the patient who experienced
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Table 1. Characteristics of the five patients involved in the study

<table>
<thead>
<tr>
<th>ID</th>
<th>Age and gender</th>
<th>NRTI mutations at baseline</th>
<th>NNRTI mutations at baseline</th>
<th>PI mutations at baseline</th>
<th>INSTI mutations at baseline</th>
<th>HIV-1 tropism at baseline</th>
<th>Genotypic sensitivity score</th>
<th>CD4+ T-cell count at baseline, cells/µl</th>
<th>HIV RNA at baseline, copies/ml</th>
<th>Optimal background regimen</th>
<th>DTG concentration, ng/ml</th>
<th>CD4+ T-cell count at 48 weeks, cells/µl</th>
<th>HIV RNA at 48 weeks, copies/ml</th>
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<td>1</td>
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<td></td>
<td>348</td>
<td>800</td>
<td>TDF/FTC; ATV/c, MVC</td>
<td>20,082</td>
<td>488</td>
<td>&lt;40</td>
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</tbody>
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*Baseline = initiation of dolutegravir (DTG) 100 mg twice daily. Calculated also including the analysis of gp41 gene. Switched to emtricitabine/tenofovir alafenamide (F/TAF) during follow-up. ATV, atazanavir; ATV/c, atazanavir/cobicistat; ATV/r, atazanavir/ritonavir; CCR5, C-C chemokine receptor type 5; CCR6, C-X-C chemokine receptor type 6; DRV, darunavir/ritonavir; INSTIs, integrase strand transfer inhibitors; MVC, maraviroc; NRTIs, non-nucleoside reverse transcriptase inhibitors; NNRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.
virological failure presented an extensive drug resistance which abolishes the effect of the employed drugs resulting in the highest viral load at baseline. The high viral burden may be responsible for the limited potential efficacy of the increased dose of DTG used. To date, all patients who suppressed viremia are still on therapy with DTG 100 mg twice daily with treatment duration ranging from 72 to 96 weeks.

Discussion

In conclusion, to the best of our knowledge, a DTG dose 2× higher than the recommended dose for INSTI resistant subjects was safely administered for the first time in five failing antiretroviral-experienced patients. We have shown that the blood drug concentration 12 h after administration is 4× that of the standard 50 mg/day dose, ruling out a solubility concern associated with this dosage. Notably, the higher DTG concentrations are associated with OBRs containing atazanavir, whereas the lower are associated with OBRs containing darunavir. This is consistent with previous studies from Song et al. showing either an increase in DTG exposure when administered with atazanavir [15] and a decrease when administered with darunavir [16]. In both cases Song et al. consider the DTG changes as ‘non-clinically significant’ with no dose adjustment necessary. Given the relatively small sample size a statistical significance could not be established. However, the fact that four out of five patients attained and maintained a long-term suppression of HIV viraemia suggests that DTG 100 mg/twice daily, in association with an OBR, could be a potential rescue therapy in patients harbouring INSTI resistant viruses mutated at position Q148 and G140. Moreover, it must be noted that the three patients which previously experienced a failing DTG 50 mg/twice daily treatment, all reached and maintained a long-term suppression of HIV viraemia.

Disclosure statement

The authors declare no competing interests.

References


