Non-virological response to a dolutegravir-containing regimen in a patient harbouring a E157Q-mutated virus in the integrase region

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Sir,

We report an observational case of a patient who had received a second kidney transplant for end-stage renal failure related to IgA nephropathy. He received thymoglobulins as induction therapy as well as steroids (10 mg of prednisone daily), mycophenolate mofetil (750 mg daily) and tacrolimus (6 mg daily) with adequate trough blood concentrations (median 7.7 µg/L). At the time of renal transplantation, hepatitis B surface antigen, hepatitis C virus and HIV-1 antibodies and HIV-1 PCR were all negative for the patient and the donor. The post-operative course was uneventful, and he had immediate graft function. One year later, he was hospitalized with weight loss, thrush, flu-like symptoms and worsening renal function without graft rejection.

Then, HIV-1 antibodies were detected (Architect system Ag/Ab VIH Combo, Abbott) with a plasma viral load of 6.3 log10 copies/mL (Roche COBAS Ampliprep/COBAS Taqman HIV-1 Test v2.0) and 131 CD4 T cells/mm3. A western blot profile indicated an HIV-1 primary infection (subtype B) without opportunistic infections or hepatitis B and C coinfections.

In this HLA-B*5701-negative patient with primary HIV-1 infection with high plasma viral load who received immunosuppressive treatment responsible for drug–drug interactions, raltegravir at 400 mg twice daily and abacavir/lamivudine at standard doses were administered to avoid the risk of proximal tubulopathy induced by tenofovir.

Fifteen days after ART initiation, the flu-like symptoms disappeared. After 5 months on the raltegravir-containing regimen, plasma viral load persisted at 3.9 log10 and the CD4 T cell gain was 351 cells/mm3 (Figure 1a). All antiretroviral trough plasma concentrations, determined using liquid chromatography coupled with tandem MS (Acquity UPLC-TQD; Waters, Milford, MA, USA), were adequate at each visit, suggesting good adherence (Figure 1a). No resistance-associated mutation was found in the reverse transcriptase or protease genes. The only mutation that was found was in the integrase gene (E157Q). This mutation confers resistance to raltegravir according to the French ANRS algorithm. Retrospectively, genotypic resistance testing on the pre-therapeutic sample showed that the E157Q mutation was already present, explaining the non-virological response to this raltegravir-containing regimen.

Raltegravir was then switched to dolutegravir (50 mg twice daily). Six weeks later, despite an adequate dolutegravir trough plasma concentration (3004 ng/mL), plasma viral load was stable at 3.6 log10 (Figure 1a). A lack of adherence was excluded because of an adequate trough plasma concentration for dolutegravir, raltegravir and tacrolimus, the absence of graft rejection and the fact that the patient was compliant with monitoring. A new genotypic resistance testing was then performed, showing no new mutations in either the integrase or the reverse transcriptase gene. This treatment was changed to 600/100 mg of darunavir/ritonavir twice daily and abacavir and lamivudine were continued, to achieve a plasma viral load of 2.7 log10 4 months after the switch.

E157Q has not yet been described to impact susceptibility to dolutegravir. A phenotypic study was then performed to explore the possible impact of the integrase gene of the patient’s virus, encompassing the E157Q mutation, on dolutegravir susceptibility. This gene was amplified and cloned in order to express the recombinant protein. Protein activity and its susceptibility to dolutegravir were compared with the WT pNL4.3 protein. Our data demonstrated that strand-transfer activity of integrase from the patient was 3-fold greater (Figure 1b). As expected, the IC50 value adjusted for protein binding was similar to historical data (22 nM) for WT pNL4.3 protein virus. For the recombinant virus with the patient’s integrase, the IC50 value was increased (198 nM). A 9-fold factor of resistance was found compared with the pNL4.3 protein (Figure 1b). Consequently, the phenotypic inhibitory quotient of dolutegravir (ratio of trough plasma concentration of dolutegravir/IC50) was 37.92, demonstrating a high level of resistance.

Dolutegravir has been reported to have a higher resistance barrier and can be effective in highly treatment-experienced populations with integrase strand transfer inhibitor-resistant virus. It has not yet been shown to select for resistance mutations in antiretroviral-naïve patients experiencing virological failure. Nevertheless, some mutations could be selected on dolutegravir at virological failure in treatment-experienced patients, including patients with raltegravir- and/or elvitegravir-resistant HIV, typically with a history of Q148 mutation. Some mutations selected by

Figure 1. In vivo and in vitro resistance to dolutegravir. (a) Evolution of plasma viral load, CD4 T cell count and plasma antiretroviral concentrations in the patient. RAL C12 h, raltegravir plasma concentration (ng/mL) 12 h after oral twice-daily dose. G-RAL C12 h, raltegravir metabolite plasma concentration (ng/mL) 12 h after oral twice-daily dose. DTG C12 h, dolutegravir plasma concentration (ng/mL) 12 h after oral twice-daily dose. ABC C24 h, abacavir plasma concentration (ng/mL) 24 h after oral once-daily dose. 3TC C24 h, lamivudine plasma concentration (ng/mL) 24 h after oral once-daily dose. pVL, plasma HIV-1-RNA (log10 copies/mL). NA, not available. (b) In vitro dolutegravir (DTG) susceptibility of the WT and patient integrase strand transfer (ST) reaction of both integrases. (Left-hand panel) The ST reaction was performed using a 32P-labelled oligonucleotide mimicking the pre-processed substrate indicated by an arrow. Products of the reaction were loaded on a 16% acrylamide/urea gel and quantified using ImageQuant 4.1 software. Products of the reaction are indicated (ST products). Drug concentrations are indicated above each lane. IN, integrase. IN+EDTA is the negative control. The percentage of ST activity of the patient’s integrase was normalized against WT activity (bottom panel). One representative experiment out of three independent experiments is indicated. (Right-hand panel) Percentages of WT integrase and the patient’s integrase activity without dolutegravir.
raltegravir could be associated with resistance to dolutegravir.\textsuperscript{6,9} None of the mutations associated with dolutegravir resistance\textsuperscript{9} was present in the HIV integrase in this patient. Nevertheless, we cannot exclude the possible presence of an unknown mutation associated with resistance to dolutegravir.

We have described a case of non-virological response to a dolutegravir-containing treatment in a patient harbouring an E157Q-mutated virus in the integrase region in the context of appropriate therapeutic adherence, without newly acquired mutations during treatment with a combination of ART, including raltegravir and dolutegravir, reinforcing the need for genotypic resistance testing of the integrase gene in all naive patients. The resistance of dolutegravir was confirmed phenotypically in vitro. More data are needed to better define the dolutegravir resistance profile in order to avoid jeopardizing future therapeutic options with next-generation integrase inhibitors.

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F. D. reports grants from Sanofi, MSD and Abbvie, outside the submitted work. G. P. has received travel grants, consultancy fees, honoraria or study grants from various pharmaceutical companies, including Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViIV Healthcare and Splicos. O. L. has been a consultant for Gilead Sciences, a speakers’ bureau member for Pfizer, Novartis, Astellas, Merck and Gilead Sciences, and has received research grants from Gilead Sciences. V. A.-F. reports travel grants and honoraria from BMS and Gilead, outside the submitted work. C. D. has received travel grants, honoraria or study grants from various pharmaceutical companies, including Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViIV Healthcare. E. B., E. T., F. L., A. S. and O. D.: none to declare.

References