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SHORT COMMUNICATION

Dolutegravir-Based Antiretroviral Regimens for HIV Liver Transplant Patients in Real-Life Settings

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Abstract

Background and Objectives Liver transplantation is now considered a safe procedure in patients with HIV because of the advent of potent antiretroviral therapies (ART).

Objective We aimed to describe the use of dolutegravir-based maintenance ART in patients with HIV and liver transplant regularly followed in our hospital.

Methods We searched the database of our Department of Infectious Diseases for liver transplant recipients receiving calcineurin inhibitor-based maintenance immunosuppression concomitantly treated with dolutegravir for at least 1 month.

Results Ten HIV-positive liver transplant recipients were identified. At 4.6 ± 3.5 years post-transplant, all the patients were switched to dolutegravir-based therapies for treatment simplification. However, at 1 year after the switch, five of the ten patients returned to their previous ART regimens because of increased serum transaminases ($n = 1$), reversible increased serum creatinine ($n = 4$), repeated episodes of nausea/vomiting ($n = 1$) and variable out-of-range concentrations of tacrolimus or cyclosporine ($n = 2$). However, it should be recognized that these events cannot be unequivocally ascribed to dolutegravir and, in the case of increased serum creatinine, are predictable.

Conclusions The management of HIV-positive liver transplant recipients in clinical practice is a complex task, where possibility of simplifying antiretroviral regimens must be balanced with the need to guarantee optimal immunosuppression and the finest treatment tolerability. A multidisciplinary approach involving physicians and clinical pharmacologists/pharmacists could help achieve this goal.

1 Background

Liver transplantation is now considered a safe procedure in select HIV-positive patients with end-stage hepatic disease because of the advent of potent antiretroviral therapies (ART) [1, 2]. Moreover, potential concerns related to drug–drug interactions (DDIs) between immunosuppressive agents and ART have been overcome by the availability of booster-free, integrase inhibitor-based regimens, which are now considered first-line ART according to international guidelines [3, 4]. Indeed, raltegravir is exclusively metabolized by uridine 5′-diphospho-glucuronosyltransferase and is neither an inducer nor an inhibitor of cytochrome P450 (CYP)-3A4 and 3A5, the phase I enzymes mainly involved in the metabolism of calcineurin inhibitors. Conversely, elvitegravir requires the coadministration of cobicistat, a pharmaco-enhancer specifically designed to inhibit the CYP3A-mediated metabolism that is likely to affect the metabolism of both cyclosporine and tacrolimus and eventually increase their toxicity [3, 4]. Dolutegravir, a recent integrase inhibitor, may represent an attractive option for HIV-positive liver transplant recipients because of its

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Key Points

Liver transplantation is considered a safe procedure in selected HIV-positive patients with end-stage hepatic disease because of the advent of potent antiretroviral therapies.

Dolutegravir, a second-generation integrase inhibitor, may represent an attractive option for HIV-positive liver transplant recipients because of its minimal dependence on cytochrome P450 (CYP)-3A-mediated metabolism, high potency and high genetic barrier.

Our findings that 50% of patients from our database who had switched to dolutegravir returned to their previous regimens indicates the complexity of therapy management in HIV-positive liver transplant recipients in real-life settings.

minimal dependence on CYP3A-mediated metabolism, high potency and high genetic barrier [3, 4]. However, data on the use of dolutegravir in real-life transplant settings are limited and exclusively involve kidney transplant recipients [5–9]. Here, we sought to describe the use of dolutegravir-based maintenance ART in HIV-positive liver transplant patients regularly followed in our hospital.

2 Materials and Methods

2.1 Subject Population

We searched the database of our Department of Infectious Diseases (with more than 6000 HIV-positive patients actively followed-up) for liver transplant recipients receiving calcineurin inhibitor-based maintenance immunosuppression concomitantly treated with dolutegravir for at least 1 month. Demographic and clinical information was also collected, together with data on therapeutic drug monitoring of immunosuppressive trough concentrations.

2.2 Statistical Analyses

The frequency distribution data are expressed as percentages, and all other measures are expressed as means ± standard deviation. All statistical analyses were performed in MEDCALC, Software (Mariakerke, Belgium). A P value < 0.05 was considered statistically significant.

2.3 Ethics Statement

This retrospective study was conducted using data collected for clinical purposes, all of which had been previously made anonymous in accordance with the requirements of the Italian Personal Data Protection Code (Legislative Decree No. 196/2003) and the general authorizations issued by the Italian Data Protection Authority. Ethics committee approval was unnecessary because Italian law states it is only required for prospective clinical trials of medical products for clinical use (Arts. 6 and 9 of Legislative Decree No. 211/2003). All patients provided informed consent for the medical procedures used for routine treatment purposes.

3 Results

Ten HIV-positive liver transplant recipients were identified (nine men, one woman, mean age 57 ± 3 years) who received a transplant 6.0 ± 3.1 years previously (see Table 1 for detailed information). Reasons for liver transplantation were hepatocellular carcinoma ($n = 2$), hepatitis C ($n = 5$) or hepatitis B/delta-virus-related end-stage liver cirrhosis ($n = 3$). The immunosuppressive therapy consisted of tacrolimus ($n = 4$) or cyclosporine ($n = 6$); two of the ten patients were also given everolimus. For ART, patients were receiving tenofovir disoproxil fumarate/emtricitabine ($n = 7$) combined with raltegravir ($n = 5$), dolutegravir ($n = 1$) or unboosted fosamprenavir ($n = 1$); the remaining three patients were receiving abacavir/lamivudine/raltegravir, atazanavir/ritonavir/raltegravir or darunavir/ritonavir/raltegravir, respectively.

At 4.6 ± 3.5 years post-transplant, all the patients switched to dolutegravir-based therapies for treatment simplification. At 1 year after the switch, five of the ten patients returned to their previous ART for several reasons (Table 1). Specifically, patient 1 experienced progressive increases in serum aspartate aminotransferase (from 38 to 78 IU/L) and alanine aminotransferase (from 19 to 100 IU/L) in the first 3 months after the switch to dolutegravir that was also associated with variable and unpredictable tacrolimus trough concentrations (reaching a nadir of 1.1 ng/mL then increasing to 22.9 ng/mL as shown in Fig. 1a) despite prompt tacrolimus dose adjustments (ranging from 0.5 to 1.5 mg daily). Patient 9 experienced increased serum creatinine concentrations (from 0.8 to 1.8 mg/dL before and after conversion to dolutegravir) associated with variable and unpredictable cyclosporine trough concentrations (reaching a nadir of 59 ng/mL as shown in Fig. 1b), despite prompt cyclosporine dose adjustments (ranging from 50 to 125 mg twice daily). Patients 6 and 10 experienced increased serum creatinine concentrations (from 1.3 to 1.8 mg/dL and from

Table 1 Demographic and clinical characteristics of the ten HIV-positive liver transplant recipients

Patient	Sex	Age	Year of tx	Immunosuppressive therapy	ART early post-tx	ART maintenance post-tx	Post-tx follow-up
1	M	63	2007	Tacrolimus	TDF/FTC/uFPV	TAF/FTC/DTG	Increment of serum transaminases (+100–400%), variable tacrolimus concentrations, switched to TAF/FTC/uFPV
2	M	57	2010	Cyclosporine	ABC/3TC/RAL	ABC/3TC/DTG	DTG-based HAART maintained
3	M	57	2010	Tacrolimus/everolimus	TDF/FTC/RAL	TAF/FTC/DTG	DTG-based HAART maintained
4	M	60	2011	Cyclosporine	TDF/FTC/RAL	TAF/FTC/DTG	DTG-based HAART maintained
5	M	52	2012	Cyclosporine/everolimus	TDF/FTC/RAL	TAF/FTC/DTG	DTG-based HAART maintained
6	M	58	2014	Cyclosporine	ATV/r/RAL	ATVr/DTG	Increment of serum creatinine (+38%), some cyclosporine dose adjustments, switched back to ATVr/RAL
7	F	55	2015	Tacrolimus	DRVr//RAL	DRVc/DTG	Increment of serum creatinine (+23%), nausea and vomiting, switched back to DRVr//RAL
8	M	57	2015	Cyclosporine	TDF/FTC/DTG	TAF/FTC/DTG	DTG-based HAART maintained
9	M	55	2016	Cyclosporine	TDF/FTC/RAL	TAF/FTC/DTG	Increment of serum creatinine (+125%), variable cyclosporine concentrations, switched to TAF/FTC/RAL
10	M	55	2016	Tacrolimus	TDF/FTC/RAL	TAF/FTC/DTG	Increment of serum creatinine (+55%), switched to TAF/FTC/RAL

3TC lamivudine, *ABC* abacavir, *ART* antiretroviral therapy, *ATV* atazanavir, *c* cobicistat, *DRV* darunavir, *DTG* dolutegravir, *F* female, *FPV* fosamprenavir, *FTC* emtricitabine, *HAART* highly active ART, *M* male, *r* ritonavir, *RAL* raltegravir, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate, *Tx* transplantation, *u* unboosted

1.1 to 1.7 mg/dL, respectively, before and after conversion to dolutegravir). Moreover, patient 6 had their cyclosporine dose changed several times (ranging from 10 to 50 mg twice daily). Patient 7 experienced repeated episodes of nausea/vomiting associated with increased serum creatinine (from 1.3 to 1.6 mg/dL before and after conversion from raltegravir/darunavir/ritonavir to dolutegravir/darunavir/cobicistat). Clinical conditions and laboratory examinations improved in all five patients after returning to the initial ART. In all circumstances, the decisions to modify the ART regimens were made by the infectious disease physicians after consultation with the transplant physicians and were not guided by specific pharmacy algorithms.

4 Discussion

To the best of our knowledge, this is the first report on the use of dolutegravir-based ART in HIV-positive liver transplant recipients on stable maintenance immunosuppression. The case of a renal transplant recipient in whom a switch from a protease inhibitor-based regimen to dolutegravir led to subtherapeutic tacrolimus concentrations and increased serum creatinine was recently published [5]. Of course, in this case, the reduction of tacrolimus concentrations was related to the discontinuation of ritonavir, which has a well-known boosting effect on tacrolimus metabolism/disposition, and not to dolutegravir. However, it does provide another example of the difficulty of managing immunosuppressive therapy in HIV-positive transplant recipients.

Here, we documented that, at 1 year after the switch to dolutegravir, 50% of the liver transplant patients identified from our database returned to their previous ART for several reasons. However, it should be recognized that the safety concerns cannot be univocally ascribed to dolutegravir, except for the observed increment in serum transaminases in one liver transplant recipient, an uncommon effect already reported for dolutegravir [10]. Four additional patients experienced increased serum creatinine, which is a known "cosmetic" effect of dolutegravir [3, 4]. Indeed, dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function [2]. Therefore, this change does not reflect renal toxicity or worsening renal function, and infectious diseases physicians who start a dolutegravir-containing regimen should expect this change and advise their patients. Conversely, increased serum creatinine concentration is also a well-known side effect of cobicistat and calcineurin inhibitors [11, 12]. This can be challenging from a clinical viewpoint in transplant patients who are receiving

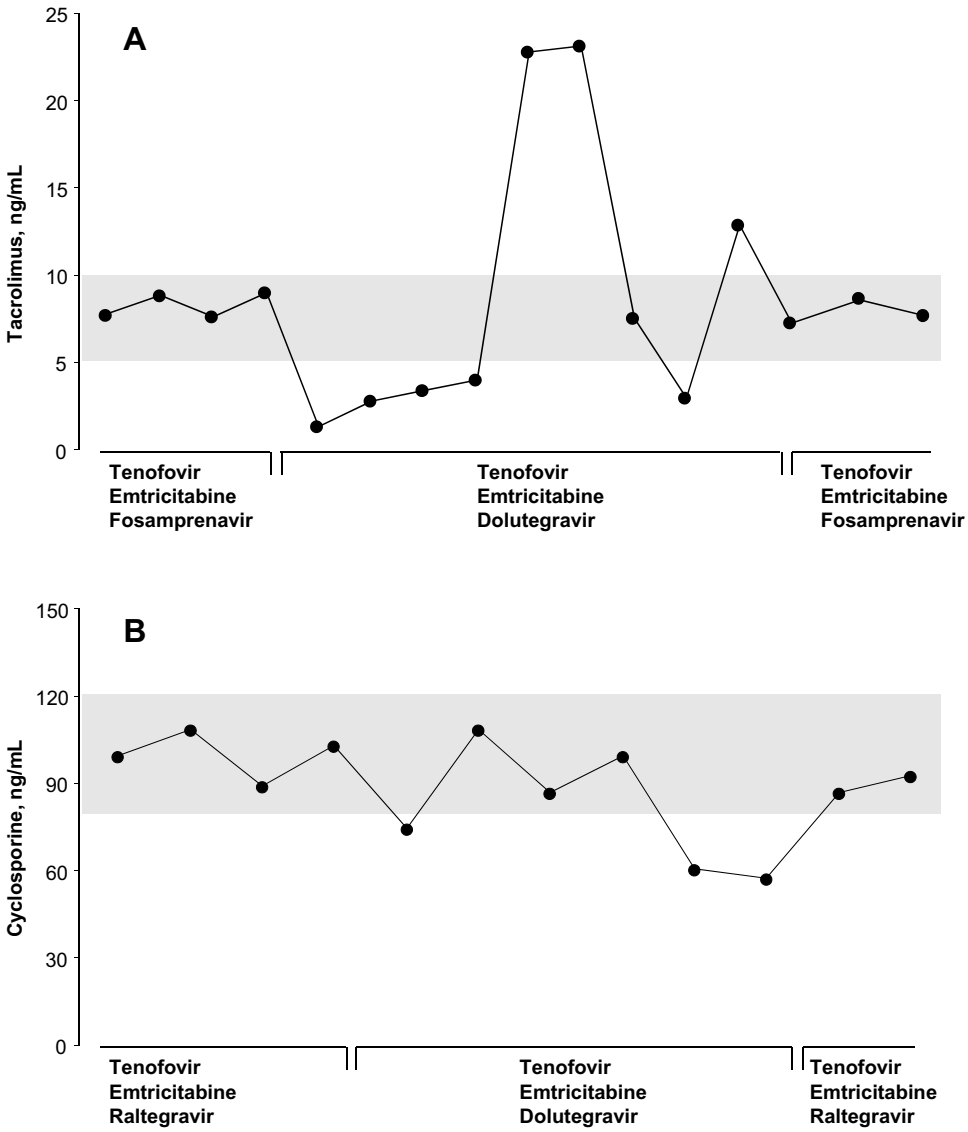

Fig. 1 Time course of tacrolimus (**a**) or cyclosporine (**b**) trough concentrations measured in two HIV-positive liver transplant recipients before, during and after the switch to dolutegravir-based antiretroviral therapies. All therapeutic drug monitoring assessments were done at steady state conditions (at least a week after immunosuppressant dose adjustment). Shaded areas represent therapeutic ranges of immunosuppressive trough concentrations adopted in our center

immunosuppressive therapy with calcineurin inhibitors, which can also often cause serum creatinine increases but as a result of nephrotoxicity [8]. Equally, the episodes of nausea/vomiting can be caused by many different DDIs or specific drug toxicities, such as dolutegravir, ritonavir or cobicistat (as in the case of patient 7). Therefore, a causal association between dolutegravir use and the reported episodes of drug-related adverse events cannot be established, and this is beyond the scope of the present investigation. This study was not intended to investigate the tolerability of dolutegravir in a liver transplant setting; we solely intended to provide evidence on the difficulty of managing therapies in patients with complex polypharmacy, such as HIV-positive liver transplant recipients, in clinical practice.

Significant fluctuations in tacrolimus and cyclosporine concentrations (despite prompt drug dose adjustments) were observed in two patients immediately after the switch to dolutegravir. This is an unexpected finding. Indeed, in vitro investigations have shown that dolutegravir has a low propensity to cause DDIs given its neutral effect on metabolic enzymes and drug transporters (with the exclusion of organic cation transporter-2 [OCT2] [3, 4]). However, some unanticipated DDIs involving dolutegravir have recently been reported and attributed to unknown mechanisms [13, 14]. These findings, together with ours, suggest that the potential for dolutegravir DDIs in real-life settings needs to be better characterized. Nevertheless, we cannot exclude that variable calcineurin inhibitor concentrations may be related to adjustments in drug dosage performed by transplant physicians based on the observed increase in serum creatinine concentrations (being unaware that this increase is caused by the inhibition of OCT2 by dolutegravir rather than being a reflection of an aggravation of renal function). Therefore, it is likely that the expected change in serum creatinine

concentrations was unanticipated by transplant physicians unfamiliar with these effects. It would have been helpful to know who made the immunosuppressive dose adjustments; however, this information was not available in our database, and this is the main limitation of the present study. This lack of information is because HIV-positive transplant patients are followed in our hospital for the management of HIV treatment but the immunosuppressive therapy is managed by individual transplant centers from other hospitals (the Luigi Sacco Hospital does not have a transplant program). We can only speculate that, if the immunosuppressive doses were not changed in consultation with pharmacists, clinical pharmacologists or transplant infectious disease physicians, this could have led to inappropriate adjustments in immunosuppression, causing further problems. Finally, a potential contribution of fosamprenavir discontinuation on the observed variable tacrolimus exposure cannot be ruled out, at least in patient 1. Indeed, it has been reported that fosamprenavir, although less potent than other HIV protease inhibitors, may significantly inhibit tacrolimus clearance [15].

5 Conclusions

Balancing the possibility of simplifying ART with the need to guarantee optimal immunosuppression and finest treatment tolerability in HIV-positive liver transplant recipients in clinical practice is a complex task. A multidisciplinary approach involving physicians and clinical pharmacologists/pharmacists could help in achieving this goal.

Author contributions DC and CG supervised all the stages of the study and wrote the first draft of the manuscript. MF performed pharmacokinetic analyses and revised the draft manuscript. SS, PM, DM and LM cared for the liver transplant patients and revised the draft manuscript.

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Compliance with Ethical Standards

Conflict of interest Dario Cattaneo, Salvatore Sollima, Paola Meraviglia, Laura Milazzo, Davide Minisci, Marta Fusi, Carlo Filice and Cristina Gervasoni declare no potential conflicts of interest with respect to the research, authorship and/or publications of this article.

Ethical approval This retrospective study was conducted using data collected for clinical purposes, all of which had been previously made anonymous in accordance with the requirements of the Italian Personal Data Protection Code (Legislative Decree No. 196/2003) and the general authorizations issued by the Italian Data Protection Authority.

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