CASE REPORT

Complex drug interactions in an HIV-seropositive heart transplant recipient

HIV seropozitif kalp transplant alıcısında kompleks ilaç etkileşimleri

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Summary– Highly active antiretroviral therapy has led to greater life expectancy for human immun-deficiency virus (HIV)-positive patients. This was a report of 11 years of follow-up of an HIV-seropositive patient who underwent heart transplantation in 2006, with emphasis on the management challenges of complex drug interactions over time.

Özet– Son derece aktif antiretroviral tedavi, insan immün yetmezliği virüsü (HIV) pozitif hastalar için daha uzun yaşam beklentisini mümkün kılmıştır. Zaman içinde kompleks ilaç etkileşimlerinin yönetim zorluklarına vurgu yapan bu rapor 2006 yılında kalp nakli yapılan HIV seropozitif bir hastanın 11 yıllık takip raporudur.

The first heart transplantation in an HIV-seropositive recipient was reported in 2003.[1,2] Only a few cases have been described since then, mainly with a limited focus on short- or mid-term follow-up. The potential of drug interaction between antiretroviral and immunosuppressive agents is well established and can lead to toxic levels of drugs, organ rejection, or HIV progression to AIDS. Presently described is the case of an HIV-seropositive patient who underwent heart transplantation, with an emphasis on the management challenges of complex drug interactions over time.

Abbreviations:

CNI	*Calcineurin inhibitor*
HAART	*Highly active antiretroviral therapy*
II	*Integrase inhibitor*
PI	*Protease inhibitor*
NRTI	*Nucleoside reverse transcriptase inhibitor*

CASE REPORT

The patient is a 47-year-old man with a long history of valvular cardiomyopathy. He underwent a double valve replacement (aortic and mitral) in 1984 and contracted HIV through blood transfusions received perioperatively. When he was referred to our center in 2006, he presented with severe dilated cardiomyopathy (left ventricular end diastolic and systolic dimension of 70 mm and 60 mm, respectively) and a left ventricular ejection fraction of 15%. Antiretroviral therapy had been initiated in 1994, and the patient had been using highly active antiretroviral therapy (HAART) since 1997. He had no history of opportunistic infection. At the time of heart transplantation in September 2006, he had been treated with zidovudine, lamivudine, and abacavir for the 3 years prior.

During follow-up, he had 1 episode of acute focal rejection (International Society for Heart and Lung

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Transplantation grade 1A). There was also 1 episode of detectable viral load (147 copies/mL), which was associated with the nadir of his CD4 count (165 cells/mm3). At that point, the antiretroviral therapy was modified, and a normal CD4 count and undetectable viral load were achieved. He never developed an opportunistic infection after heart transplantation. In 2017, an echocardiogram showed no significant abnormality, and a coronary angiogram revealed mild to moderate coronary disease.

After transplantation, the HAART regimen had consistently been composed of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs). In follow-up, the composition of his HAART changed several times, mainly because of disabling side effects of an antiretroviral therapeutic agent. The immunosuppressive therapy was initially based on low doses of tacrolimus, in addition to mycophenolate mofetil and prednisone, which were discontinued after only a few months. Adjustment of the tacrolimus dose was particularly challenging, with highly fluctuating serum levels. We used doses as low as 0.1 mg once weekly to try to maintain adequate targeted concentrations (10–15 ng/mL in the first 2 months, 8–12 ng/mL between months 3–6, and 5–10 ng/mL thereafter). In September 2011, 5 years post-transplantation, the use of tacrolimus was terminated and cyclosporine was initiated. At that time, the tacrolimus dose was 0.07 mg every other day, and cyclosporine was started at a dose of 3 mg every other day. We used a dose ratio of 1 mg of tacrolimus for 40 mg of cyclosporine for the conversion. After a few weeks, we relied on maintenance doses cyclosporine of 20 mg in the morning and 10 mg in the evening to reach the targeted cyclosporine serum level of 100–200 ng/mL. Since then, the dose of cyclosporine has been modified on only 4 occasions, 1 of which was related to a change in antiretroviral therapeutic agent. Significantly fewer interactions and more stable serum concentrations were seen with the use of cyclosporine compared with tacrolimus. The complete drug regimen history is shown in Table 1.

Table 1. Drug regimen history of the patient

	HAART regimen	Immunosuppressive therapy	CNI serum concentration
Immediate post-transplant period	Abacavir 600 mg daily Lamivudine 300 mg PO daily Stavudine 40 mg PO daily Atazanavir 400 mg PO daily	Tacrolimus 0.5 mg twice daily MMF 750 mg twice daily Prednisone 22.5 mg daily	TAC >20 ng/mL
January 2007 (4th month)	Id.	Tacrolimus 0.5 mg daily MMF 1 g twice daily Prednisone 15 mg daily	TAC 13-15 ng/mL
May 2007 (8th month)	Trizivir (abacavir, lamuvidine and zidovudine) 1 tablet twice daily Ritonavir 100 mg daily	Tacrolimus 0.4 to 0.1 mg daily MMF 250 mg twice daily Prednisone discontinued	TAC 12-13 ng/mL
July 2007 (10th month)	Abacavir 600 mg daily Lamivudine 400 mg daily Ritonavir 100 mg twice daily Fosamprenavir 700 mg twice daily	Tacrolimus 0.1 mg once weekly, increased until 0.25 mg once daily MMF discontinued	TAC 4.4-7.8 ng/mL
Between August 2007 and December 2010 (11th month to 51st month)	Abacavir 600 mg daily Lamivudine 400 mg daily Darunavir 600 mg twice daily Ritonavir 100 mg twice daily	Tacrolimus 0.2 mg every other day decreased gradually until 0.07 mg every other day	TAC 5.4-19.8 ng/mL

Table 1. Drug regimen history of the patient *(cont.)*

	HAART regimen	Immunosuppressive therapy	CNI serum concentration
January 2011 to September 2011 (52nd month to 60th month)	Truvada (tenofovir 300 mg and emtricitabine 200 mg) 1 CO daily Darunavir 600 mg twice daily Ritonavir 100 mg twice daily	Tacrolimus 0.07 mg every other day	TAC 8.5-10.3 ng/mL
September 2011 (69th month)	Id.	Tacrolimus discontinued Cyclosporine 3 mg every other day, increased gradually to 20 mg daily (September 3 to September 30)	CsA <50 ng/mL At the end of September: CsA around 100 ng/mL
October 2011 (61st month)	Id.	CsA 20 mg AM and 10 mg PM	CsA around 130 ng/mL
May 2012 (66th month)	Raltegravir 400 mg twice daily Etravirine 200 mg twice daily Ritonavir 100 mg twice daily Darunavir 600 mg twice daily	Id.	CsA around 180 ng/mL
November 2013 to August 2016 (86th month to 119th month)	Id.	CsA 10 mg twice daily	CsA 226 ng/mL before dose reduction, CsA 72-164 ng/mL afterwards
September 2016 (120th month)	Darunavir 800 mg daily Genvoya 1 tablet daily (Elvitegravir 150 mg + Cobicistat 150 mg+ Emtricitabine 200 mg + Tenofovir 10 mg)	CsA 25 mg twice daily	CsA 151 ng/mL
November 2016 (122nd month)	Id.	CsA 20 mg AM and 10 mg PM	CsA 296 ng/mL before dose reduction, CsA 89-123 ng/mL afterwards
March 2017 (126th month)	Id.	CsA 25 mg AM and 10 mg PM	CsA 94 ng/mL before dose increase, CsA 88-155 ng/mL afterwards

In bold: Drugs with high potential for interaction with CNIs. In italic: Drugs with mild potential for interaction with CNIs.
CNI: Calcineurin inhibitor; CsA: Cyclosporine; HAART: Highly active antiretroviral therapy; Id: idem; MMF: Mycophenolate mofetil; PO: Per os; TAC: Tacrolimus.

DISCUSSION

HAART is typically composed of PIs, NNRTIs, or integrase inhibitors (IIs) in addition to 2 NRTIs.[3] The potential for drug interactions between antiretroviral and immunosuppressive agents is well established and can lead to toxic levels of drugs, organ rejection, or HIV progression to AIDS.[4] The highest risk is with PIs, which inhibit cytochromes P450 3A4, 3A5 (CYP3A4, CYP3A5), and P-glycoprotein, both of which have an impact on the intestinal bioavailability and hepatic metabolism of calcineurin inhibitors

Table 2. Interactions between antiretroviral drugs and immunosuppressive agents used

Antiretroviral categories	Examples of drugs	Metabolism pathway	Potential interactions		
			CNIs	MMF	mTOR inhibitors
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir, lamuvidine, stavudine, zidovudine, tenofovir, emtricitabine	Renal metabolism Abacavir: metabolized by alcohol dehydrogenase	None	None	None
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Etravirine, efavirenz	Substrates and low inducers of CYP3A4	↓ [CNIs]	None	↓ [mTOR inhibitors]
Protease inhibitors (PIs)	Atazanavir, ritonavir, fosamprenavir, darunavir, cobicistat	Strong inhibition of cytochrome CYP3A4 and Pgp	↑↑↑ [CNIs]	None	↑↑↑ [mTOR inhibitors]
Integrase inhibitors (IIs)	Raltegravir, elvitegravir	UGT-mediated glucoronidation	None	None	None
Pharmacokinetic enhancer	Cobicistat	Strong inhibition of cytochrome CYP3A4	↑↑↑ [CNIs]	None	↑↑↑ [mTOR inhibitors]

CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil; mTOR inhibitor: Target-of-rapamycin inhibitor; Pgp: P-glycoprotein; UGT: Uridine 5'-diphospho-glucuronosyltransferase.

(CNIs).4 The most potent CYP3A4 inhibitors are PI boosters, such as ritonavir and cobicistat.[5] These interactions require important dose reductions of cyclosporine and tacrolimus, 2 CNIs.[6] The NNRTIs are substrates and inducers of CYP3A4, which can lead to increased elimination of CNIs, but few dose adjustments appear to be necessary. NRTIs are mainly excreted by the kidneys and there are no interactions with immunosuppressive drugs. The new IIs, like raltegravir and elvitegravir, are metabolized primarily through hepatic glucuronidation.[3,4] However, elvitegravir is always used with cobicistat and then interacts with CNIs. Mycophenolate mofetil is metabolized by uridine diphosphate glucuronosyltransferase and is generally not involved in drug-drug interactions with antiretroviral agents. The target-of-rapamycin inhibitors, another immunosuppressive drug category that includes sirolimus, also inhibit CYP3A4 and P-glycoprotein and interact with antiretroviral agents in the same way as CNIs.[3,4] These interactions are summarized in Table 2.

This case demonstrates that there were fewer drug interactions using cyclosporine in conjunction with HAART than tacrolimus. This is consistent with previous studies that have shown that smaller doses and reductions in dosing intervals were possible with cyclosporine compared with tacrolimus.[5–8] Tacrolimus pharmacokinetics are more affected by PIs than cyclosporine.[6] In comparison with non-HIV patients, the AUC/dose exposure significantly increased in the presence of PIs and this effect persisted over time.[6] The volume of distribution, clearance, and bioavailability are also much more affected by tacrolimus than cyclosporine.[6] Moreover, cyclosporine seems to have a positive immunological effect against HIV.[9–11] Some studies have suggested that cyclosporine might reduce the incorporation of HIV-DNA in CD4 cells.[12,13] Cyclosporine also inhibits T lymphocyte activation and it has been associated with an increase in CD4 count.[10,11] Considering all of these facts, cyclosporine could be a better choice in HIV patients, especially when facing difficult drug adjustments.

Currently available data show that HIV-positive transplant recipients have favorable outcomes.[14] Nonetheless, heart transplantation remains rare in this patient population, and HIV seropositivity is still considered a contraindication in many centers. Based on the results reported here and those previously reported in the literature, we think that HIV status should no longer be a criterion for the exclusion

of potential heart transplant candidates. However, it is important to keep in mind the high potential for drug interactions, and to closely monitor serum concentrations. According to our results, when used in association with PIs, cyclosporine is a more stable immunosuppressive drug than tacrolimus and could represent a better choice. Moreover, antiretroviral agents with fewer interactions with CNIs, like IIs and CCR5 antagonists, are now available for HIV treatment and should be considered for transplant patients.[4,15]

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