CASE: Switch to Ibalizumab in Suppressed Person with HIV with Immunosuppressive Drug-Drug Interactions After Liver Transplant

Lucas Hill[1], Heather Hoang[1] ,Saima Aslam[1], Janice Kerr[1], Maile Young[1]

[1]*University of California San Diego, San Diego, USA*

UC San Diego Health

Introduction

- The 2015 HIV Organ Policy Equity (HOPE) Act permitted organ transplantation between HIV-positive donors and recipients, allowing life-saving treatment for people with HIV (PWH) who have end-organ disease and organ failure.[1]
- While there are increased opportunities for transplant, PWH have added layers of complexity relating to resistance profiles and drug-drug interactions (DDIs) between their antiretroviral (ARV) regimen and the immunosuppressive medications required to prevent organ rejection.
- Ibalizumab (IBA), a CD4-directed post-attachment HIV-1 inhibitor, received US approval in 2018 as the first long-acting antiretroviral and monoclonal antibody for HIV-1 treatment.[2]
- IBA is a first-in-class agent indicated in combination with other ARVs for the treatment of HIV infection in heavily treatment-experienced adults that have multidrug resistant HIV-1 infection and are failing their current ARV regimen. [2]
- No known DDIs have been identified between IBA and other medications. [2]

Patient History

DEMOGRAPHICS AND HIV HISTORY

- The patient is a 58-year-old white male diagnosed with HIV in 1992. He has been on 17 subsequent HIV regimens since 1995.
- CD4 nadir of 35 cells/mm^3 and a history of Pneumocystis pneumonia in 2005.
- Undetectable viral load (HIV-1 RNA ≤50 copies/mL) since 2008.
- Current ARV regimen is dolutegravir/lamivudine (DTG/3TC) and boosted darunavir (DRV/c) daily.

KEY CLINICAL CHALLENGES

- The patient has a history of nodular regenerative hyperplasia cirrhosis complicated by hepatocellular carcinoma requiring liver transplantation.
- The main challenge was to construct a suppressive ARV regimen without DDIs with his immunosuppressive medications, the primary concern being DDIs between DRV/c, tacrolimus, and prednisone.
- Unfortunately, previous resistance testing as well as proviral testing from September 2015 showed multiple resistance patterns. Separate testing revealed enfuvirtide resistance and dual-tropic virus.

Table 1. Summary of all Resistance Mutations and Assessment

Class	Resistance-associated mutations	Stanford database interpretation
NRTI	M41L, E44D, D67N, K70K/R, V118I, L74I/V, M184M/V, T215Y, K219Q/R/W	High level resistance: ABC, ddI, 3TC, FTC, d4T, ZDV, TDF
NNRTI	A98A/G, K101K/E, V108I, Y181Y/C, G190G/S	High level resistance: DOR, EFV, ETR, NVP, RPV
PI	L10F/I, V11V/I, I13V, D30N, L33I, M36M/I, M46I, I54V, I62I/V, L63P, A71V, T74S, I84V, N88D, L90M	High level resistance: ATV/r, FPV/r, IDV/r, LPV/r, NFV, SQV/r, TPV/r Low level resistance: DRV/r
INSTI	None	Sensitive: DTG, EVG, RAL

Patient History (cont.)

ADDITIONAL MEDICAL HISTORY

- Other diagnoses include chronic kidney disease, hypertension, depression, anal dysplasia, and bilateral DVT (2016).

Clinical Values and Therapy

Table 2. Lab values, antiretroviral therapy, and immunosuppressant regimen post-transplant

Days since transplant	Viral load (copies/mL)	CD4 (%)	CD4 count (cells/mm^3)	Tacrolimus trough (ng/mL)	ART	Immunosuppressants
0	Liver Transplantation Initiated tacrolimus 1 mg daily, MMF 500 mg BID, methylpred taper. Continued on DTG/3TC and DRV/c daily.					
7	UD	25	118	13.7	DTG/3TC daily, DRV/c daily	tacrolimus 1.5 mg daily, prednisone 20 mg daily
10	-	-	-	12.1	DRV/c discontinued, IBA q2w initiated, continue DTG/3TC daily	tacrolimus 0.5 mg daily, prednisone 20 mg daily
12	-	-	-	7.3	IBA q2w, DTG/3TC daily	tacrolimus 1.5 mg BID, prednisone 20 mg daily
18	UD	-	-	10.1	IBA q2w, DTG/3TC daily	tacrolimus 9 mg BID, prednisone 20 mg daily
24	UD	19	63	12.9	IBA q2w, DTG/3TC daily	tacrolimus 10 mg BID, prednisone 20 mg daily
31	UD	26	154	13.0	IBA q2w, DTG/3TC daily	tacrolimus 9 mg BID, prednisone 20 mg daily
41	UD	18	77	11.2	IBA q2w, DTG/3TC daily	tacrolimus 9 mg BID, MMF 500 mg BID, prednisone 50 mg daily
45	-	23	122	12.6	IBA q2w, DTG/3TC daily	tacrolimus 9 mg BID, MMF 500 mg BID, prednisone 50 mg BID
46	72	17	44	20.1	IBA q2w, DTG/3TC daily	No changes
55	UD	-	-	12.0	IBA q2w, DTG/3TC daily	tacrolimus 9 mg BID, MMF 250 mg BID, prednisone 40 mg BID
59	UD	-	-	13.1	IBA q2w, DTG/3TC daily	No changes
73	UD	19	108	10.4	IBA q2w, DTG/3TC daily	tacrolimus 9 mg BID, MMF 250 mg BID, prednisone 30 mg BID

ART=antiretroviral therapy, UD=undetectable, MMF=mycophenolate mofetil, DTG=dolutegravir, 3TC=lamivudine, DRV/c=darunavir/cobicistat, IBA=ibalizumab, q2w=every 2 weeks, BID=twice daily

ARV Switch and Outcomes

- Successful liver transplantation occurred in June 2020 at UC San Diego.
- Post-transplant, boosted darunavir (DRV/c) was changed to ibalizumab (IBA).
  - IBA was selected primarily due to its lack of expected DDIs or baseline resistance and well-tolerated profile.
  - The patient remained on dolutegravir/lamivudine (DTG/3TC) and boosted darunavir (DRV/c) from day 0 to day 10 after transplant due to difficulty accessing IBA while inpatient.
  - From day 10 onwards, IBA was administered in combination with DTG/3TC.
- The patient has maintained virologic suppression after transplantation.
- Tacrolimus levels stabilized after initial immunosuppressant dose adjustments.
- No DDIs or safety issues have been reported by the patient or treating physicians related to ARVs or immunosuppressants post-transplant.
  - Other current concomitant medications include amlodipine 10 mg PO daily, atovaquone 1500 mg PO daily, diclofenac gel 1% apply to affected area BID, enoxaparin 70 mg subq BID, furosemide 20 mg daily, metoprolol 12.5 mg PO BID, omeprazole 20 mg PO daily, sildenafil 100 mg PO prn, and trazodone 50 mg PO prn.

Discussion

- Ibalizumab is the first long-acting antiretroviral and monoclonal antibody approved for the treatment of HIV-1 infection.
- With its novel mechanism of action and high specificity towards the CD4 receptor, ibalizumab has no expected DDIs with immunosuppressive drugs or cross-resistance to other antiretrovirals.
- In this patient, the transition from boosted darunavir to ibalizumab post-transplant allowed maintenance of virologic suppression and stabilization of immunosuppression levels.
- This is notably the first documentation of IBA use in a person with HIV that has undergone liver transplantation. The combination of DTG/3TC and IBA was well tolerated by the patient.

References

1. National Institutes of Health (NIH). Federal Register. November 25, 2015. https://www.govinfo.gov/content/pkg/FR-2015-11-25/pdf/2015-30172.pdf

2. Trogarzo® (ibalizumab-uiyk) Prescribing Information, April 2022.