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Impact of Coadministration of Letermovir on Isavuconazole Plasma Concentration in Allogeneic Hematopoietic Cell Transplant (HCT) Recipients

Y. Su[1], J. Algazaq[1], A. Stern[1], H. Dumke[1], G. Papanicolaou[1, 2]
[1] Infectious Disease Service, Memorial Sloan Kettering Cancer Center , New York, United States
[2] Department of Medicine, Weill Cornell Medical College, New York, United States

Memorial Sloan Kettering Cancer Center

OBJECTIVES

There is paucity of data on coadministration of isavuconazole (ICZ) with letermovir (LET) in allogeneic hematopoietic cell transplant (HCT) recipients.

We compared ICZ plasma concentration (C_{trough}) in HCT recipients with and without coadministration of LET.

METHODS

The study cohort consists of adult HCT recipients who participated in an open label study of ICZ antifungal prophylaxis from 6/1/2017 to 10/31/2018 with ≥1 ICZ C_{trough} measured at steady state on oral ICZ.

ICZ started by Day 9 post HCT and continued until Day 70-100 based on risk for fungal infection. Since 12/15/2017 CMV seropositive HCT recipients received LET prophylaxis.

ICZ C_{trough} was compared between patients with and without concomitant administration of LET.

The impact of GI GVHD on ICZ C_{trough} was examined among who had C_{trough} measured during acute GI GVHD.

Relevant groups were compared using Chi-squared tests (Fisher's tests) and Mann-Whitney U tests, as appropriate.

RESULTS

Of 89 patients analyzed, 20 (22%) patients received concomitant LET. Baseline characteristics were similar between no-LET and LET groups.

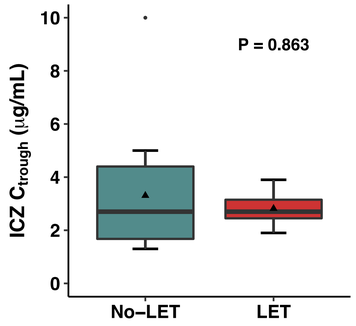
A total of 109 ICZ C_{trough} were obtained at a median of 31 (interquartile range [IQR] 23-41) days from HCT.

Baseline characteristics were similar between no-LET and LET groups.

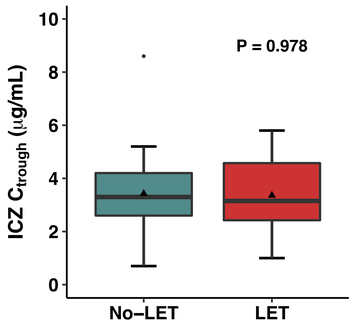
Characteristics	Overall	No-LET	LET	P value
	N = 89	N = 69	N = 20	
Age, years				0.673
Median (IQR)	57 (50-66)	57 (51-66)	58 (47-64)	
Gender, N (%)				0.139
Female	28 (31)	19 (28)	9 (45)	
Donor type, N (%)				0.260
Matched related/unrelated	54 (61)	45 (65)	9 (45)	
Mismatched related/unrelated	23 (26)	16 (23)	7 (35)	
Haploidentical	12 (13)	8 (12)	4 (20)	
Conditioning intensity, N (%)				0.605
Non-myeloablative	12 (13)	10 (14)	2 (10)	
GvHD prophylaxis, N (%)				0.086
Ex vivo T-cell depletion	29 (33)	23 (33)	6 (30)	
CyA + MMF	16 (18)	10 (14)	6 (30)	
Post CY + MMF + TAC/SRL	18 (20)	12 (17)	6 (30)	
TAC + MMF + MTX	26 (29)	24 (35)	2 (10)	

Abbreviations:
CyA: Cyclosporine; MMF: Mycophenolate Mofetil; MTX: Methotrexate;
Post CY: Cyclophosphamide; SRL: Sirolimus; TAC: Tacrolimus

(C) ICZ C_{trough} among GI GVHD

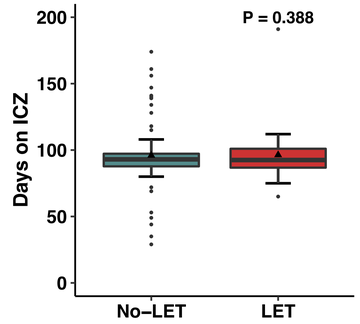


(D) ICZ C_{trough} among no GI GVHD

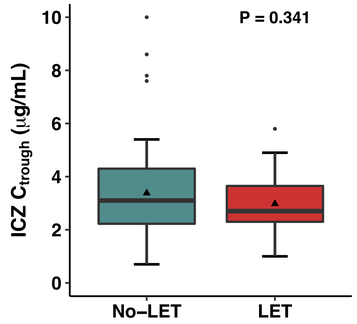


ICZ days and ICZ C_{trough} were similar between no-LET and LET groups.

(A) Total ICZ days



(B) ICZ C_{trough}



In LET group, ICZ levels were obtained after 16 (IQR 2-22) days from LET initiation. The median C_{trough} was 3.0 (IQR 2.2-4.2) µg/mL for all patients. ICZ C_{trough} were similar between LET and no-LET groups.

Twenty patients with GI GVHD had 27 ICZ C_{trough}. ICZ C_{trough} were similar in patients with and without GI GVHD (median 2.7, IQR: 1.9-3.8 µg/mL versus median 3.3, IQR: 2.5-4.2 µg/mL, respectively; p=0.089).

CONCLUSION

There was not premature discontinuation of isavuconazole due to drug interaction with letermovir.

ICZ C_{trough} were similar with and without concomitant letermovir.

Isavuconazole provides an alternative azole with less drug-drug interaction pharmacokinetic variability for HCT recipients including those with GI GVHD.

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