4CPS-118

REAL CLINICAL IMPACT OF DRUG-DRUG INTERACTIONS OF IMMUNOSUPPRESSANTS IN TRANSPLANT PATIENTS

A.I. Gago-Sánchez [1], M. Cárdenas [1], M.D. Aumente [1], P. Font [2], J.R. Del Prado [1], M.A. Calleja [3]
[1]Pharmacy Department. Reina Sofía Universitary Hospital. Córdoba/IMIBIC/University of Córdoba, Spain
[2]Rheumatology Department. Reina Sofía Universitary Hospital. Córdoba/IMIBIC/University of Córdoba, Spain
[3]Pharmacy Department. Virgen Macarena Universitary Hospital. Sevilla, Spain

Background

The risk of interaction in transplant patients is extremely high as they are polymedicated patients. Characteristics of immunosuppressants constitute an added risk. There are many potential drug-drug interactions (DDIs)but it would be interesting to know which ones are real and have clinical outcomes.

Aim and objectives

The main objective of this study was to determine the prevalence of the DDIs between immunosuppressants and other drugs with real clinical impact, categorize the type of DDIs, identify drugs involved and propose alternative therapeutic strategies improving the clinical outcome the transplant patients.

Material and methods

- ✓ A prospective, observational 1-year study (February 2018 to February 2019) was conducted at a third-level hospital including all transplanted patients and which had been prescribed at least: cyclosporin (CsA), tacrolimus (TAC), mycophenolate mofetil (MMF), everolimus (EVE) and/or sirolimus (SRL). To determine the real clinical DDIs, we evaluated data of monitoring trough blood concentrations (C_0) of immunosuppressive drugs and adverse drug events (ADEs) caused by DDIs.
- ✓ The clinical importance of the real DDIs was expressed in terms of patient outcomes: patients with ADEs due to real DDIs.
- ✓ DDIs were classified in C, D or X according to the Lexi-interact score (C=monitor therapy, D=consider therapy modification, X=avoid combination).
- ✓ The data were analyzed using SPSS v.17.0, Chicago Illinois.

Results

Table 1: **Clinical and demographic characteristics of the cohort.**

Gender N (%)	
Male	216 (69.95)
Female	93 (30.1)
Age (years) Mean ±SD (range)	52.03±14.68 (13-79)
Hospital stay (days) Mean ±SD (range)	11±7.2 (6-42)
Causes of hospitalization N (%)	
De novo transplants	132 (42.72)
Fever	64 (20.71)
Diarrhea	30 (9.70)
Respiratory infection	28 (15.53)
Hypertension	17 (5.82)
Urinary infection	8 (5.50)
Others	30 (9.70)
Comorbidities N (%)	
Hypertension	198 (64.07)
Diabetes mellitus	103 (33.33)
Dyslipidemia	82 (26.53)
Coronary heart disease	30 (9.7)
Connective tissue disease	27 (11.97)
Infectious disease	23 (8.73)
Hyperuricemia	17 (5.5)
Type of transplant N (%)	
Kidney transplant	116 (37.5)
Liver transplant	59 (19.1)
Bone marrow transplant	49 (15.9)
Lung transplant	46 (14.8)
Heart transplant	39 (12.6)

All the patients (n=309) presented potential DDIs

Nº of potential DDIs : 609

Potential DDIs (Lexi-interact): C (371 (60.91%))

CsA: 340 potential DDIs (54.05%)
TAC: 183 potential DDIs (29.09%)

Real DDIs : 67 patients

Nº of real DDIs : 71

Real DDIs (Lexi-interact): D (52 (73.23%))

TAC: 37 real DDIs (52.11%)
CsA: 28 real DDIs (39.43%)

Prevalence of real DDIs: 21.68%

Omeprazole-CsA: 78 potential DDIs, 2 real DDIs

Voriconazole-CsA: 38 potential DDIs, 20 real DDIs

Nifedipine-TAC: 59 potential DDIs, 10 real DDIs

Voriconazole-TAC: 23 potential DDIs, 11 real DDIs

Fluconazole-TAC: 25 potential DDIs, 11 real DDIs

Patient outcomes

Risk factors

A statistically significant linear correlation:
Number of prescribed drugs, real and clinical important DDIs:
Pearson correlation coefficient (r) 0.163 ($p<0.05$)

Clinical Outcome

- **Nephrotoxicity** (12%)
- **Hyperkalemia** (10%)
- **Hypertension** (5%)

Therapeutic strategies by hospital pharmacist

Recommendations for management of real DDIs

C class:
- ✓ Closely monitoring of immunosuppressant blood concentrations.
- ✓ Monitoring of blood pressure, electrolytes y blood glucose.

D and X: class:
- ✓ Dose change of immunosuppressant.
- ✓ Consider therapy modification.
- ✓ Using paracetamol instead of non-steroidal antiinflammatory.

Table 2:Drug pairs involved in real DDIs

	CYCLOSPORINE			*TACROLIMUS*			*EVEROLIMUS*			*SIROLIMUS*		
	No.IR[a]	%[b] CI 95%	Severity	No.IR[a]	%[b] CI 95%	Severity	No.IR[a]	%[b] CI 95%	Severity	No.IR[a]	%[b] CI 95%	Severity
Allopurinol	1	1.50% (0.3-7.9)	D	-	-	-	-	-	-	-	-	-
Amiodarone	-	-	-	1	1.50% (0.3-7.9)	C	-	-	-	-	-	-
Diltiazem	-	-	-	2	3.00% (0.8-10.2)	C	-	-	-	-	-	-
Fluconazole	2	3.00% (0.8-10.2)	C	11	16.40% (9.4-27)	D	2	3.00% (0.8-10.2)	D	1	1.50% (0.3-7.9)	D
Itraconazole	-	-	-	1	1.50% (0.3-7.9)	D	-	-	-	-	-	-
Nifedipine	-	-	-	10	14.90% (8.3-25.3)	C	-	-	-	-	-	-
Omeprazole	2	3.00% (0.8-10.2)	C	-	-	-	-	-	-	-	-	-
Phenytoin	2	3.00% (0.8-10.2)	D	-	-	-	-	-	-	-	-	-
Rifampicin	1	1.50% (0.3-7.9)	D	1	1.50% (0.3-7.9)	D	2	3.00% (0.8-10.2)	D	-	-	-
Voriconazole	20	29.90% (20.2-41.6)	D	11	16.40% (9.4-27)	D	2	3.00% (0.8-10.2)	X	-	-	-

Number of actual interactions, frequency and severity according to the Lexi-interact score, with respect to the sample of patients with actual drug interaction (n = 67 patients).

Abbreviations: [a] No. IR: number of real interactions; [b]% (CI 95%): frequency expressed as a percentage (95% confidence interval).

Table 3:Mean ± standard deviation variation in trough immunosuppressant blood concentrations (C), daily immunosuppressant dose (D) and C/D ratio

	CYCLOSPORIN			TACROLIMUS			EVEROLIMUS			SIROLIMUS		
	Dose Mean± SD	*Concentration Mean± SD*	*C/D ratio Mean± SD*	*Dose Mean± SD*	*Concentration Mean± SD*	*C/D ratio Mean± SD*	*Dose Mean± SD*	*Concentration Mean± SD*	*C/D ratio Mean± SD*	*Dose Mean± SD*	*Concentration Mean± SD*	*C/D ratio Mean± SD*
Without fluconazole	210±56.57	175.05±106.28	0.79±0.29	6.05±2.78*	8.96±4.18*	1.91±1.54*	2.88±3.01	3.22±0.11	2.51±2.66	1	7.7	7.7
With fluconazole	175±35.36	286.05±112.71	1.60±0.32	4.64±2.73*	15.82±5.71*	5.16±4.67*	2.25±2.47	8.97±2.00	11.32±13.34	1	11	11
Without itraconazole	-	-	-	4	8.4	2.1	-	-	-	-	-	-
With itraconazole	-	-	-	3	10.5	3.5	-	-	-	-	-	-
Without voriconazole	290.5±129.5*	184.84±89.39*	0.67±0.23*	6.32±3.19*	9.5±3.72*	1.88±1.20*	1.5±0	3.67±0.57	2.45±0.38	-	-	-
With voriconazole	194.7±78.5*	329.81±92.35*	1.89±0.85*	2.82±1.6*	14.52±4.68*	7.05±4.77*	1±0	9.40±0.40	9.41±0.40	-	-	-
Without amiodarone	-	-	-	0.5	13	26	-	-	-	-	-	-
With amiodarone	-	-	-	0.5	20	40	-	-	-	-	-	-
Without diltiazem	-	-	-	11±9.99	11.2±0.14	1.70±1.52	-	-	-	-	-	-
With diltiazem	-	-	-	6±5.66	29.2±5.8	7.94±6.52	-	-	-	-	-	-
Without nifedipine	-	-	-	9.55±4.39*	10.24±5.53*	1.28±0.89*	-	-	-	-	-	-
With nifedipine	-	-	-	7.5±4.06*	17.14±13.19*	3.11±3.09*	-	-	-	-	-	-
Without phenytoin	140±42.43	146.35±6.38	1.10±0.38	-	-	-	-	-	-	-	-	-
With phenytoin	165±33.36	74±23.48	0.44±0.05	-	-	-	-	-	-	-	-	-
Without rifampicin	50	65.8	1.31	1	2.1	2.1	0.5	3.2	6.4	-	-	-
With rifampicin	150	17.4	0.11	1	0.1	0.1	0.5	1.62	3.24	-	-	-
Without omeprazole	225±106.07	133.15±36.98	0.62±0.13	-	-	-	-	-	-	-	-	-
With omeprazole	225±106.07	277.95±62.01	1.32±0.35	-	-	-	-	-	-	-	-	-
Without allopurinol	125	60.9	0.48	-	-	-	-	-	-	-	-	-
With allopurinol	100	92.6	0.92	-	-	-	-	-	-	-	-	-

Statistically significant difference: * $p < 0.01$

Abbreviations: Mean ± SD: mean ± standard deviation; C/D ratio: trough immunosuppressant blood concentrations (measurement units: ng/ml) / daily immunosuppressant dose (measurement units: mg)

Conclusion

There are many potential interactions described in the literature but only a small percentage proved to be real DDIs,based on the patients´ outcomes,which were detected by determining the variations in C_0 of immunosuppressants and ADEs of patients caused by DDIs. Few patients suffered ADEs due to the close pharmacokinetic monitoring of immunosuppressants.The results found allow us to identify the pharmacological groups that caused real DDIs.

https://www.eahp.eu/25-4CPS-118