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CLINICAL PHARMACOKINETICS OF EVEROLIMUS IN LUNG TRANSPLANTATION: STRATEGIES OF MONITORING

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BACKGROUND

Therapeutic monitoring of everolimus is necessary to determine an optimal dosage regimen in lung transplantation patiens to prevent graft rejection due to the narrow therapeutic window. The area under the concentration-time curve (AUC0-12) is the best strategy for the pharmacokinetic study because reflects the total drug exposure in the body, especially in cystic fibrosis (CF) patients, who have abnormalities of the gastrointestinal system.

PURPOSE

To evaluate the absorption profile of everolimus in patients with CF after lung transplantation in order to optimize the immunosupresive therapy.

MATERIAL AND METHODS

Pharmacokynetic, descriptive and cross-sectional study was conducted in lung transplantation patients with a determination of AUC0-12 of everolimus at less than four months post-transplantation. After seven days minimum of receiving the same dose, nine blood samples were collected at predose, 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-morning dose. The target trough levels were 3-8 ng/mL. Everolimus exposure was evaluated according to the dosage. Everolimus serum concentration was measured by QMS Immunoassay.

Table 1. Characteristics of the patients

Patient	Age (Years)	Weight (kg)	Treatment
1	17	46	EVE 1,25/1,25 mg + TAC 4/4 mg
2	29	44	EVE 1,5/0,75/1,5 mg + TAC 3/3/3 mg
3	26	54	EVE 1,5/1mg + MPA 360/360 mg
4	18	47	EVE 1,75/1,75 mg + TAC 5/5 mg
5	40	56	EVE 1,25/1,25 mg + TAC 2,5/2,5 mg
6	13	28	EVE 1,5/1,5 mg + TAC 2,5/2,5 mg
7	29	67	EVE 1,75/1,75 mg + TAC 3/3 mg
Median	26	47	
Range	13-40	28-67	

EVE: everolimus; TAC: tacrolimus; MPA: mycophenolate sodium

RESULTS

Seven full pharmacokynetics analyses were performed in bilateral lung transplant patients (Table 1). All of them were women. Two patients showed a normal absorption profile of everolimus and five patients showed a low overall exposure to everolimus because the value Cmin and AUC0-12 is below the normal range (Table 2). All this patients underwernt dose/interval modification of everolimus after results. Following the adjustment, all patients reached levels within therapeutic range.

Table 2: Pharmacokinetics parameters

Patient	Cmin (ng/mL)	Cmax (ng/mL)	Tmax (h)	Css (ng/mL)	AUC0-12 (ng·h/mL)
1	1.62	6.40	1	2.57	30.81
2	2.00	7.70	6	6.63	53.10
3	3.45	5.74	2	4.18	50.21
4	1.86	5.64	2	2.85	34.30
5	1.97	6.38	2	4.50	54.02
6*	4.58	16.30	1	9.44	113.31
7*	4.51	18.51	1	7.02	84.28
Median	2.00	6.40	2	4.50	53.10
Range	1.62-4.58	5.6-18.5	1-6	2.57-9.44	30.8-113.3

Cmin: trough concentration; Cmax: peak exposure; Tmax; time to reach peak exposure; Css: steady-state concentration; AUC: area under the curve
(*): Patients who showed normal absorption profile of everolimus

CONCLUSIONS

The pharmacokynetics variability of everolimus is very high. Monitoring of everolimus levels could optimize immunosupresive therapy. The AUC0-12 will be calculated at any CF patients regardless time after transplantation as long as they are not trough levels in the therapeutic range.

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