PHARMACOGENETICS AS A TOOL IN DOSE ADJUSTMENT OF IMMUNOSUPPRESSIVE DRUGS: A CASE REPORT

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BACKGROUND

Tacrolimus is an immunosuppressant drug, calcineurin inhibitor, used after transplant organ as preventive and curative treatment.
Therapeutic drug monitoring (TDM) is strongly recommended for this drug, because of its narrow therapeutic range, interpatient variability, drug interactions and toxicity depending on plasmatic concentration.

PURPOSE

We report the case of a transplant **patient who did not achieve the target residual concentration** (Cres) of tacrolimus.

MATERIALS AND METHODS

PATIENT

64 years
130 kg – 187 cm (BMI = 37 kg/m²)

- Alcohol-induced cirrhosis
- Ascites
- Hepatic encephalopathy
- Esophageal varices
- Severe portal hypertension

→ **Liver transplantation**

BIOLOGICAL AND DRUGS OUTCOMES

Peri-operative collection : *Candida albicans*
Blood culture : *Enterobacter cloacae*

Immunosuppressive therapy

- Mycophenolate mofetil
- Prednisolone
- **Tacrolimus**

(target Cres = 10-15 ng/mL)

Anti infective therapy

- Meropenem
- Caspofungin

PHARMACEUTICAL ANALYSIS

Despite tacrolimus dose ajustment, Cres was not reached

Hypotheses:

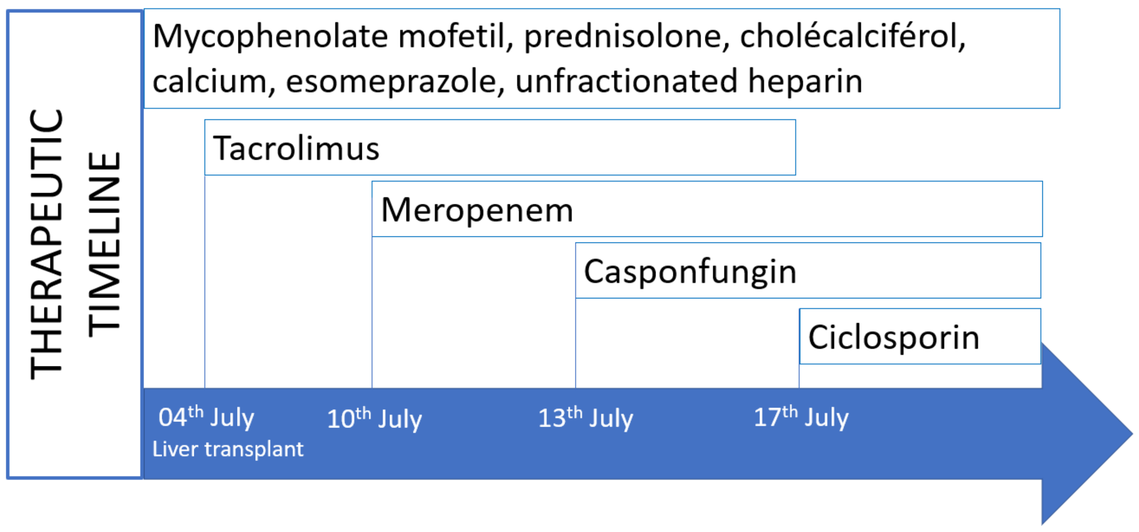
- Uncompliance
- Inappropriate sampling times
- Drug interactions
- Pharmacogenetics

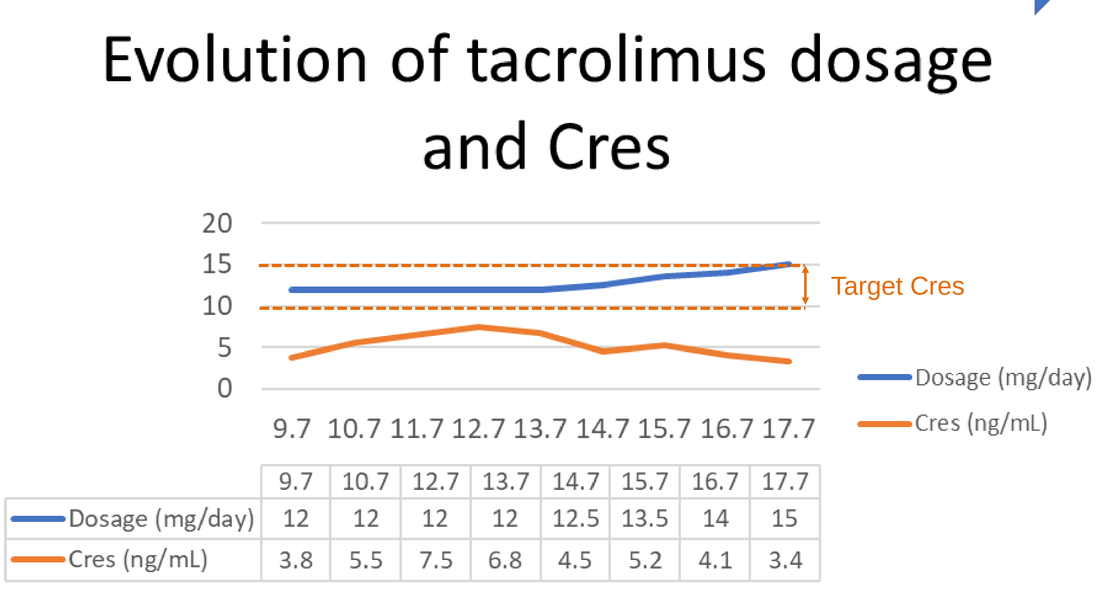
→

- Interviews with the patient
- Interviews with nurses
- Interactions : Literature review / DDI predictor / HUG cytochromes table

Keywords: *tacrolimus, caspofungin, meropenem, interactions, pharmacogenetics*

RESULTS





	9.7	10.7	12.7	13.7	14.7	15.7	16.7	17.7
Dosage (mg/day)	12	12	12	12	12.5	13.5	14	15
Cres (ng/mL)	3.8	5.5	7.5	6.8	4.5	5.2	4.1	3.4

Uncompliance and **inappropriate samplings**

Drug interactions in literature

- Tacrolimus + Ertapenem (same class as meropenem): increase of tacrolimus Cres[1] → **excluded**
- Tacrolimus + Caspofungin : decrease of tacrolimus Cres during a 10-days co-administration[2] → **insufficient** to explain the very important decrease of the Cres

Pharmacogenetics: ***CYP3A5*3*** **allele**

***CYP3A5* genotype**	***3/*3**	***3/*1**	***1/*1**
Caucasian population	90%		
Dose of tacrolimus to introduce (mg/kg/day)[3]	0.15	0.20	0.25

26th July : Mutation *3/*1
g.6986A>G

MEDICAL DECISION

Rejection risk/ long delay for pharmacogenetics results
Obese patient/ iatrogenic risk => No dosage modification

→ **Replacement of tacrolimus by ciclosporin**

CONCLUSION

Pharmacogenetics may explain some « resistance-to-treatment » occurence.
Characterization of the cytochrome 3A5 genotype can be a predictive means in tacrolimus dosage optimization allowing the achievement of effective Cres while avoiding toxic effects. Unfortunately, it is not always possible to wait for results because of their risk of transplant rejection.
It is **important to raise awareness in the medical teams about pharmacogenetics**.

References:
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