INFLUENCE OF *CYP2C19* GENOTYPES ON CITALOPRAM OR ESCITALORAM THERAPEUTIC RESPONSE

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INTRODUCTION :

- About 30 to 50% of depressed patients do not respond to initial antidepressant treatment[1].
- A recent study showed a strong impact of *CYP2C19* allelic variants on escitalopram therapeutic failures over 1 year[2].

AIM : To evaluate the clinical impact of *CYP2C19* genotype on the therapeutic failure occurring at 2, 3, 6 and 12 months after citalopram or escitalopram treatment initiation.

METHODS :

- Data were obtained from 334 patients enrolled in the PsyMetab cohort[3] and treated by citalopram or escitalopram between 2007 and 2021 and genotyped for *CYP2C19* poor (PM), extensive or intermediate (EMIM) and ultra-rapid metabolism (UM)).
- Therapeutic failure was described by one of the following :
  - Treatment stop or switch, dosages ≥20mg escitalopram OR ≥40mg citalopram OR ≤5 mg escitalopram OR ≤10 mg citalopram.
  - Adjunction of mirtazapine, lithium, aripiprazole or quetiapine to increase antidepressant response.
- A survival analysis with left truncation and right censoring was performed to study the association between therapeutic failure and genotype-based phenotypes over 2, 3, 6 and 12 months. The proportion of on treatment patients at each time point per genotype was determined. Pairs of genotypic groups were then compared using a test of Wald.

RESULTS :

Patients followed for 1 year : n = 314 (*CYP2C19* poor (PM) n=4, extensive or intermediate (EMIM) n=223, ultra-rapid metabolizers (UM) n=87)

Table 1. *Population description*

Patients characteristics		PM (n=4) n (%) or median (min; max)	EMIM (n=223) n (%) or median (min; max)	UM (n=87) n (%) or median (min; max)
Women		2 (50%)	135 (61%)	49 (56%)
Age (years)		23 (20;46)	47 (15;94)	41 (18;90)
Ethnic origin	*Caucasian*	NA	0 : 6 (2,7%)	0 : 3 (3,5%)
	Asian	3 (75%)	184 (79,0%)	73 (83,9%)
	Arabic	NA	2 : 1 (1,0%)	NA
	African (American)	NA	4 : 15 (6,7%)	4 : 4 (4,6%)
	Other	NA	5 : 17 (7,6%)	5 : 7 (8,1%)
Maintenance doses (mg/day)		1 (25%)	NA	NA
		15 (5;20)	10 (0.5;50)	10 (0;50)

Figure 1. Survival curves representing the probability of treatment response as a function of time (days)

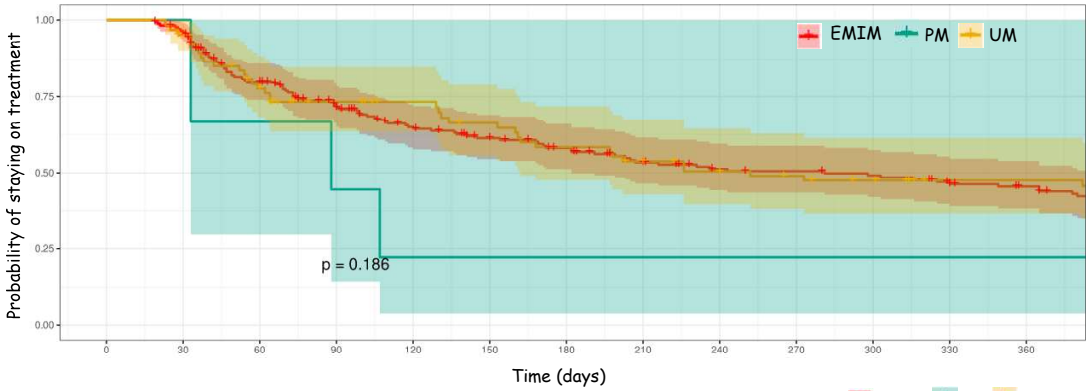

Figure 2. Survival values of phenotypes predicted by *CYP2C19* genotype as a function of time (days)**

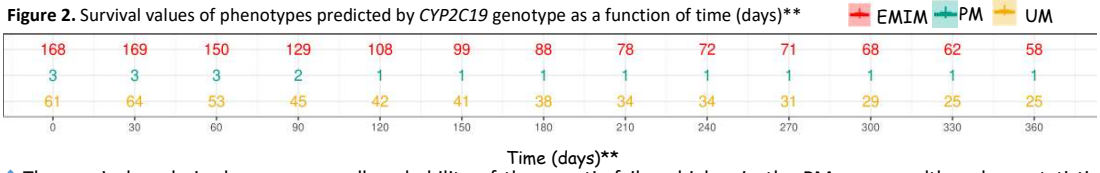

Table 2. *Comparison of the proportion still on treatment according to CYP2C19 genetics-predicted phenotypes at 2, 3, 6, and 12 months (n=314)*

Pheno1	Pheno2	%Pheno1	%Pheno2	p-value***
2 months				
EMIM	PM	79.6%	66.7%	0.665
EMIM	UM	79.6%	77.6%	0.740
3 months				
EMIM	PM	70.9%	44.4%	0.421
EMIM	UM	70.9%	73.3%	0.706
6 months				
EMIM	PM	56.8%	22.2%	0.305
EMIM	UM	56.8%	58.4%	0.827
12 months				
EMIM	PM	43.8%	22.2%	0.459
EMIM	UM	43.8%	47.4%	0.624

****Test de Wald*

***Number of people observed as a function of time*

- The survival analysis shows an overall probability of therapeutic failure higher in the PM groups, although no statistical differences was observed between the genetic groups at each time point (Table2).

CONCLUSION :

- **The small number of patients per genotypic group and the retrospective nature of the study prevented to detect a statistically significant difference in treatment failure between PM compared to EMIM and UM patients treated with citalopram or escitalopram. Neither was there any differences between the EMIM and the UM phenotype groups.**
- **A prospective randomized clinical study needs to be conducted to evaluate the potential benefit of *CYP2C19* genotyping on citalopram or escitalopram treatment success.**

[1]Lindsley CW. The top prescription drugs of 2011 in the United States: antipsychotics and antidepressants once again lead CNS therapeutics. ACS Chem Neurosci. 2012;3(8):630-1.
[2]Jukić MM, Haslemo T, Molden E, Ingelman-Sundberg M. Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. Am J Psychiatry. 2018;175(5):463-70.
[3]Dubath C, et al. "Evaluation of cardiometabolic risk in a large psychiatric cohort and comparison with a population-based sample in Switzerland." *The Journal of Clinical Psychiatry* 81.3 (2020): 2272