5PSQ009

CYP2C19 SNP´S INFLUENCE ON CLOPIDOGREL RESPONSE IN CEREBROVASCULAR DISEASE PATIENTS. FINAL RESULTS

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Background and Objective: Carrying some polymorphisms, contained in the DNA region encoding the *CYP2C19* expression, have shown a significant association with a lack of clopidogrel efficacy among coronary patients. This association had been widely researched and the clopidogrel label recommends testing the *CYP2C19* loss of function alleles before the start of the treatment, even DPWG and CPIC pharmacogenetic dosing guidelines, recommend switching clopidogrel in case of carrying the *CYP2C19* loss of function alleles in coronary patients with stent. This remains unstudied in cerebrovascular disease patients.

The aim is to explore the influence of *CYP2C19* genetic polymorphisms on clopidogrel response in cerebrovascular disease patients.

Methods: Patients after stroke or transient ischemic event (TIA) treated with clopidogrel after the hospitalization were recruited. These were tested for carrying the *CYP2C19*2, *3* (loss of function, LOF) and **17* (Gain of function, GOF) alleles. As primary endpoint we considered the combined occurrence of stroke, TIA, cardiovascular death and acute coronary syndrome (ACS). Furthermore, we collected data about clinical parameters (age, sex, ethnicity), co-medication during follow-up and vascular risk factors.

We tested the association between carrying LOF or GOF alleles and the primary endpoint in a univariate analysis, and multivariate analysis including those clinical parameters previously related to clopidogrel response. OR and HR were calculated and p-values <0.05 were considered statistically significant.

VARIABLE	Total n=67 n (%)
Diagnóstico (ICTUS)	53 (79.1)
Cirugía	8 (11.94)
Sexo (Mujeres)	24 (35.82)
Edad (Media ± DS)	68.22 ± 9.83
FACTORES DE RIESGO	
EC previa	22 (32.84)
Hipercolesterol.	48 (71.64)
HTA	53 (79.1)
Diabetes	28 (41.79)
Tabaquismo	11 (16.42)
AIT/ictus previo	28 (41.79)
Stent	9 (13.43)
TRATAMIENTO	
Antiagregante prev.	48 (71.64)
AAS	20 (29.85)
B-bloq	16 (23.88)
Estatina	52 (77.61)
IECA	26 (38.81)
ARAII	20 (29.85)
Antagonistas Ca	15 (22.39)
IBP	30 (44.78)

DS: Desviación Estándar; HTA: Hipertensión arterial; EC previa: Antecedentes de enfermedad cardiológica. TRATAMIENTO: tratamiento prescrito al alta del ingreso por el que se recluta el paciente; AAS: Ácido Acetil Salicílico, B-bloq: B-bloqueantes; HBPM: Heparinas de bajo peso molecular; IECA: Inhibidores de la enzima convertidora de angiotensina; ARAII: Antagonistas de los receptores de la angiotensina II; IBP: Inhibidores de la bomba de protones.*Test exacto de Fisher

RESULTS

	Evento primario SI n=14	Evento primario NO n=53	OR (IC 95%)	p-valor	HR (IC 95%)	p-valor
***CYP2C19* LOF n=18**	7 (38.89%)	11 (61.11%)	3.82 (1.1 - 13.2)	**0.028**	3.01 (1.01 - 9.00)	**0.048**
***CYP2C19* No LOF n=49**	7 (14.29%)	42 (85.71%)				
***CYP2C19* GOF n=24**	2 (8.33%)	22 (91.67%)	0.23 (0.02 - 1.24)	0.059	0.29 (0.06 - 1.34)	0.093
***CYP2C19* No GOF n=43**	12 (27.91%)	31 (72.09%)				

Asociación entre polimorfismos y el evento primario en pacientes con ictus/AIT

	OR (IC 95%) *	p-valor
CYP2C19 LOF	5.07 (1.2-21.45)	**0.023**
CYP2C19 GOF	0.19 (0.03-1.09)	**0.037**

http://www.eahp.eu/24-5PSQ-009

* Datos ajustados por: "antecedentes de enfermedad cardiológica", hipercolesterolemia, tratamiento concomitante con antagonistas del Ca y polimorfismos

Asociación entre polimorfismos y el evento primario en pacientes con ictus/AIT (Multivariante)

Discussion: Carrying *CYP2C19 LOF* allele was significantly associated to the primary endpoint in the single and multivariate analysis. This association remains significant if we perform a survival analysis. Carrying *CYP2C19 GOF* allele was not related to the primary endpoint in the univariate analysis, but, in the multivariate analysis, it was significantly associated with protection against the primary endpoint.

Conclusions:

- *CYP2C19 LOF* polymorphisms may be used as genetic marker of clopidogrel response in cerebrovascular disease patients.
- *CYP2C19*17* allele should be considered as a protector against the combined occurrence of stroke, TIA, cardiovascular death and acute coronary syndrome (ACS).

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