

CYTOCHROME P450 2C19 GENOTYPING FOR PERSONALISATION OF PROTON PUMP INHIBITOR THERAPY

J.L. DeBattista^{1,2}, J. Schembri³, C. Barbara², G. Zahra², F. Wirth¹, L.M. Azzopardi¹

¹Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

²Molecular Diagnostics - Infectious Diseases Unit, Department of Pathology, Mater Dei Hospital, Msida, Malta

³Gastroenterology, Department of Medicine, Mater Dei Hospital,, Msida, Malta

BACKGROUND AND IMPORTANCE

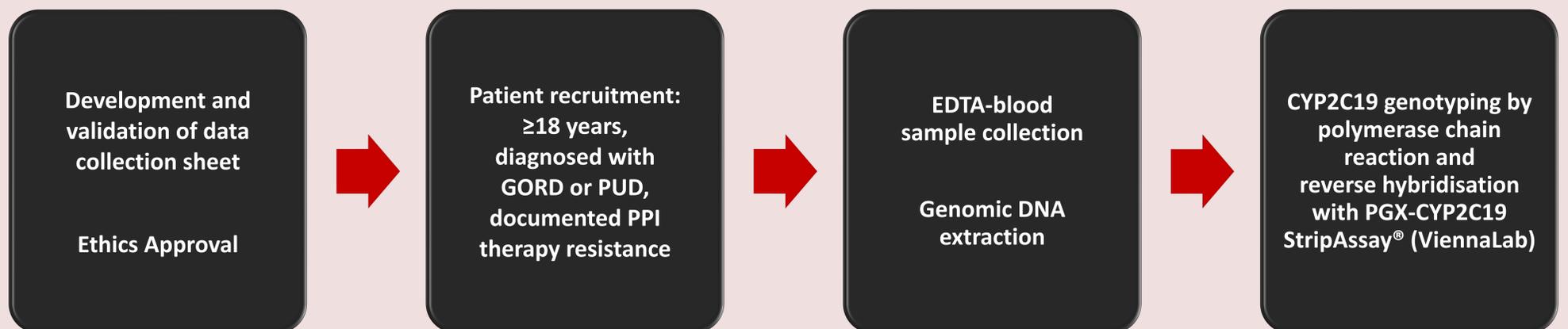
Proton pump inhibitors (PPIs) are the main class of drugs used in clinical practice for acid suppression to treat and prevent various conditions, including gastro-oesophageal reflux disease (GORD) and peptic ulcer disease (PUD). PPIs are generally considered effective, however sub-optimal response has been reported. PPIs are hepatically metabolised, primarily by the polymorphic cytochrome P (CYP) 450 2C19 enzyme. CYP2C19 genetic polymorphisms have been associated with affecting exposure and efficacy of PPIs.¹

AIM

To determine the prevalence and clinical implications of CYP2C19 genetic polymorphisms in patients receiving PPIs and demonstrating therapy resistance

METHOD

Cohort study



RESULTS

- 51 patients recruited (50 Caucasian, 1 Asian, 29 male, mode 50-59 years)
- PPI therapy: Esomeprazole (n=27; 20mg n=11, 40mg n=16), omeprazole (n=22; 20mg n=13, 40mg n=9), lansoprazole (n=2; 30mg)
- Most common PPI resistance: Reflux hypersensitivity (n=19), persistent oesophagitis despite PPI treatment (n=17)
- Most patients were genotyped as **1/*1* (n=26) (Table 1)
- No patients were genotyped as **17/*17*, ultra-rapid metabolisers
- Nineteen out of 35 patients with normal or rapid metaboliser phenotype were on standard dose (20mg) omeprazole or esomeprazole; 16 were taking a higher dose (40mg)

Table 1: Phenotype (genotype) frequencies and clinical implications (N=51)

Phenotype (Genotype)	Frequency (%)	Clinical Implications ¹
Normal metabolisers, NM (<i>*1/*1</i>)	26 (51%)	Normal PPI metabolism; May be at increased risk of therapeutic failure compared to IM and PM phenotypes
Rapid metabolisers, RM (<i>*1/*17</i>)	9 (18%)	Decreased plasma concentrations of PPIs compared to NM phenotype; increased risk of therapeutic failure
Intermediate metabolisers, IM (<i>*1/*2, *2/*17</i>)	14 (27%)	Increased plasma concentration of PPIs compared to NM phenotype; increased chance of efficacy and potential toxicity
Poor metabolisers, PM (<i>*2/*2</i>)	2 (4%)	

CONCLUSION

The majority of patients in the cohort studied demonstrating PPI therapy resistance were identified as normal or rapid metabolisers. Normal and rapid metaboliser phenotypes are associated with lower plasma exposure and risk of therapeutic failure compared to intermediate and poor metabolisers. Patients with normal or rapid metaboliser phenotype could benefit from an increase in dose or changing the PPI to one less dependent on CYP2C19 metabolism, such as rabeprazole, to enhance the likelihood of efficacy.¹ Pharmacist-led CYP2C19 pharmacogenetic testing can be beneficial in identifying patients at risk of therapeutic failure to personalise and optimise PPI therapy.

Reference

1. Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, et al. Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP2C19 and proton pump inhibitor dosing. *Clin Pharmacol Ther.* 2021; 109(6): 1417-1423. doi: 10.1002/cpt.2015.

ACKNOWLEDGEMENTS

The research work disclosed in this publication is partially funded by the Endeavour Scholarship Scheme (Malta). Project part-financed by the European Social Fund - Operational Programme II – European Structural and Investment Funds "Investing in human capital to create more opportunities and promote the well-being of society". University of Malta Research Grant PHRRP12-21.