Possible impact of factor V Leiden genotype on warfarin induced bleeding

Sir,

We read with interest the report, recently published by Nahar *et al*.[1] on the prevalence of warfarin sensitive alleles in factor V Leiden (FVL) mutation carriers. The study provides preliminary evidence for the need of pre-prescription genotyping of warfarin sensitive polymorphisms (CYP2C9*2, *3 and Vitamin-K epoxide reductase complex subunit1 [VKORC1]-1639G/A) in patients who are at risk of thrombosis (carriers of thrombophilic marker) and require anticoagulation therapy.

The authors have reported that 55.6% of the patients who carry FVL mutation also carry warfarin sensitive genotypes; thus, it is important that all patients with thrombophilia need warfarin genotyping prior to prescription with warfarin. The prevalence of these genotypes are however, not significantly different in few other studies including ours [Table 1], where the allele frequencies were studied in warfarin anticoagulated patients, as well as normal healthy controls.[2,3] FVL mutation has however, not been studied in these cases.

Table 1: Genotype and allele frequencies of CYP2C9 and VKORC1 in few studies from India

Genotypes/Alleles	Nahar *et al*.[1] (FVL carrier patients) *N*=61	Shalia *et al*.[2] (normal and patients operated for aortic or mitral valve replacement) *N*=183	Gaikwad *et al*.[3] (warfarin treated patients) *N*=145
	Frequencies *n* (%)		
CYP2C9 genotype			
CYP2C9*1/*1	41 (67.2)	126 (68.9)	105 (72.4)
CYP2C9*1/*2	6 (9.8)	17 (9.3)	9 (6.2)
CYP2C9*1/*3	13 (21.3)	35 (19.1)	27 (18.6)
CYP2C9*2/*2	0	0	0
CYP2C9*2/*3	1 (1.7)	0	0
CYP2C9*3/*3	0	5 (2.7)	4 (2.8)
VKORC1-1639G>A genotype			
GG	43 (70.5)	138 (75.5)	111 (76.6)
GA	17 (27.9)	41 (22.4)	31 (21.4)
AA	1 (1.6)	4 (2.1)	3 (2.0)
CYP2C9 allele			
CYP2C9*1	0.83	0.84	0.85
CYP2C9*2	0.06	0.04	0.03
CYP2C9*3	0.11	0.12	0.12
VKORC1 allele			
VKORC1-1639G	0.84	0.87	0.87
VKORC1-1639A	0.16	0.13	0.13

FVL: Factor V Leiden, VKORC1: Vitamin K epoxide reductase complex subunit 1, CYP2C9: Cytochrome P450 2C9

In our study, which included 145 warfarin treated patients (blinded to FVL or other thrombophilic marker carrier status), nearly 44.14% patients were found to be carriers for one or more variant genotype(CYP2C9*2, *3 and VKORC1-1639G/A). Out of these warfarin sensitive genotype carrier patients, 67.18% patients faced over anticoagulation (INR > 4) while on warfarin. Indicating that genotyping of warfarin sensitive markers will be beneficial in all the patients prior to the initiation of anticoagulation therapy.[3]

Another important aspect of coinheritance of thrombophilia is its impact on the bleeding phenotype. Several studies, both *in vitro* and case series have shown that FVL mutation modulates the clinical severity in hemophilia and other rare bleeding disorders.[4,5] We therefore premise that FVL carrier patients should be at lower risk of over anticoagulation than the FVL non-carrier patients. This would be confirmed by undertaking studies in large series of anticoagulated patients with the long duration follow-up analysis for over anticoagulation and risk of bleeding in carriers of thrombophilia marker versus non-carriers.

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