Oral

[O26-1] O26-1: Immunosuppressive drugs: assey and genotyping

Chairs: Stein Bergan, Norway / Maria Shipkova, Germany
Tue. Sep 26, 2017 10:30 AM - 11:15 AM Room C1 (1F)

(Tue. Sep 26, 2017 10:30 AM - 11:15 AM Room C1)

[O26-1-3] Is CYP3A5*3 genotyping for tacrolimus dosing really beneficial?

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Keywords: CYP3A5*3 GENOTYPING, TACROLIMUS, CPIC, INDIANS, PHARMACOGENETICS

Background

Tacrolimus is a widely used immunosuppressive drug with narrow therapeutic index and large inter-individual variability, which may lead to either graft rejection or nephrotoxicity. Blood concentrations of tacrolimus are strongly influenced by CYP3A5 genotype with CYP3A5*3 carriers tends to have high tacrolimus level than CYP3A5*1 carriers. The Clinical Pharmacogenetics Implementation Consortium (CPIC) 2015 guidelines recommends increasing the tacrolimus dose by 1.5 –2.0 times the recommended starting dose in patients with CYP3A5 *1/*3 and *1/*1, whereas in patients with CYP3A5 *3/*3, standard tacrolimus dosing is recommended. CYP3A5*3 genotyping for Tacrolimus dosing has been introduced in our hospital and the present study intends to determine the clinical utility of CYP3A5*3 genotyping in managing transplant patients on Tacrolimus therapy.

Methods

Since 2016, a total 30 samples were sent to our laboratory for CYP3A5*3 (A6986G) genotyping. Informed consent as well as detailed clinical data was collected from each patient. Genomic DNA was extracted from EDTA blood sample using the modified salting out procedure. Amplification-refractory mutation system (ARMS)–Polymerase chain reaction (PCR) was used for CYP3A5 genotyping. The genotyping results are validated by DNA sequencing. t test was carried out to determine the association between the CYP3A5*3 genotypes and the mean tacrolimus dose.

Results

CYP3A5 *1/*1(AA), *1/*3(AG) and *3/*3(GG) genotypes were found to be 33.3%, 40.7% and 25.9% respectively with variant allele(G) frequency to be 0.46. The CYP3A5*3 genotype results for each patients showed good clinical correlation. Interestingly, a five-fold reduction was seen in mean tacrolimus dose (required to achieve the therapeutic range) of patients with *3/*3 genotypes (0.027 mg/kg/day) as compared to those with *1/*1, *1/*3 genotypes (0.133 mg/kg/day). Also, the difference in the mean tacrolimus dose for patients with *1/*1, *1/*3 genotypes and those with *3/*3 was found to be extremely significant (p=0.0009).

Conclusions

Thus with significantly lower tacrolimus dose required in patients with CYP3A5*3/*3 genotype as against those with *1/*1, *1/*3 genotypes, it can be concluded that preemptive *CYP3A5*3* genotyping should be strongly considered before tacrolimus therapy in order to avoid, nephrotoxicity in *3/*3 patients as well as graft rejection in patients with *1/*1 and *1/*3 genotypes