Pattern of CYP3A5 and MDR-1 single nucleotide polymorphism and its impact on Tacrolimus levels and clinical outcomes in living renal allograft recipient

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Methodology

1. 160 live related renal transplant patients at tertiary care hospital in India were included in this study from 2016 to 2018.
2. Genetic polymorphism in CYP3A5 and MDR1 gene was carried out at time of transplant.
3. All patients were given a fixed weight based dosage of tacrolimus.
4. Data was collected and analysed in terms of Tac levels, time to therapeutic levels, major infections and rejections with respect to genotype polymorphism.

Results

1. 69.2% of Wild variants of CYP 3A5 (Fast metabolisers) have initial low tac levels
2. 51.5% of Homo variants (Slow metabolisers) have initial high tac levels.
3. All variants achieve optimum tac levels at same time (Mean 12.4 days).
4. More infections in Homo variants. Rejections not different among variants
5. No clear correlation of initial Tacrolimus level with MDR-1 variants was seen

Homovariants
Cryptococcal diarrhoea, Pulmonary Tuberculosis(2), UTI(3), Bacteremia, Esophageal candidiasis(2), Parvovirus infection, Pulmonary mucormycosis, CMV
Heterovarients
Graft Pyelonephritis Herpes Zoster, Pulmonary mucormycosis
Wild Variants
Acute Gastroenteritis

Table 2: Major Infections

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1. **Fixed dosages with TDM can lead to significant high and low initial Tac levels and higher infections in Homo variants**
2. **Time to therapeutic level was same in all variants**
3. **Rejections were not different**
4. **A larger sample with genotype based dosing is required to test such strategy**

Introduction

1.Tacrolimus has narrow therapeutic index

2. Wide variation in tacrolimus level with weight based fixed dosage regimens

3. Polymorphism of major pathways of metabolism ie CYP3A5 and MDR1

4.Fast metabolizer require higher dosage and slow metabolizer require lower dosage.

5. Genotype based dosing strategy may be useful to achieve early therapeutic level and reduce infections and rejections.

Methodology

1. 160 transplant patients, 2016 to 2018.
2. Genetic polymorphism analysis in CYP3A5 and MDR1 gene.
3. Fixed weight-based dosage of Tacrolimus.
4. Data analyzed in relation to genotype polymorphism.

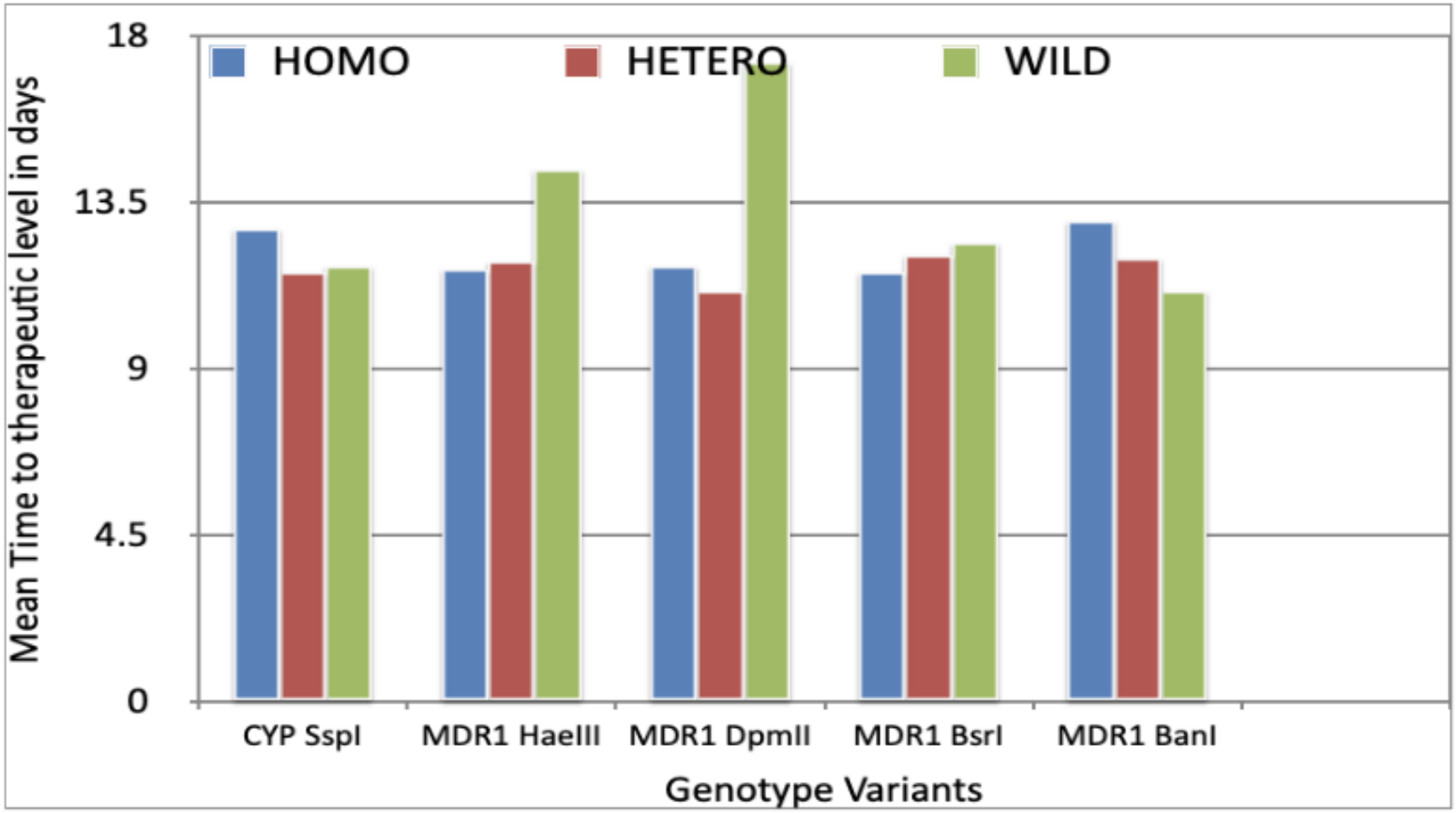

Diagram 1: Time to Therapeutic level

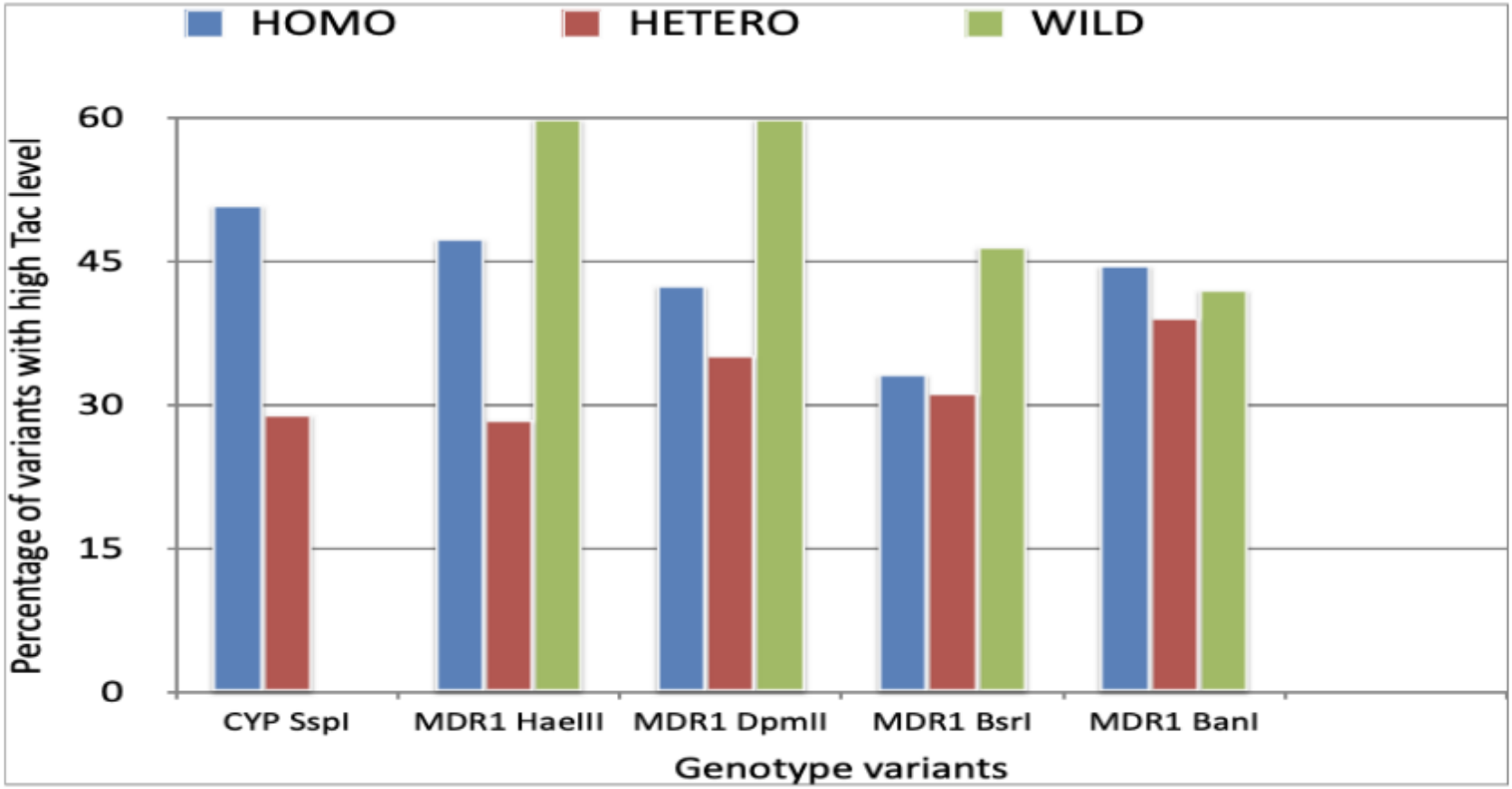

Diagram 2 : SNP and high Tac level

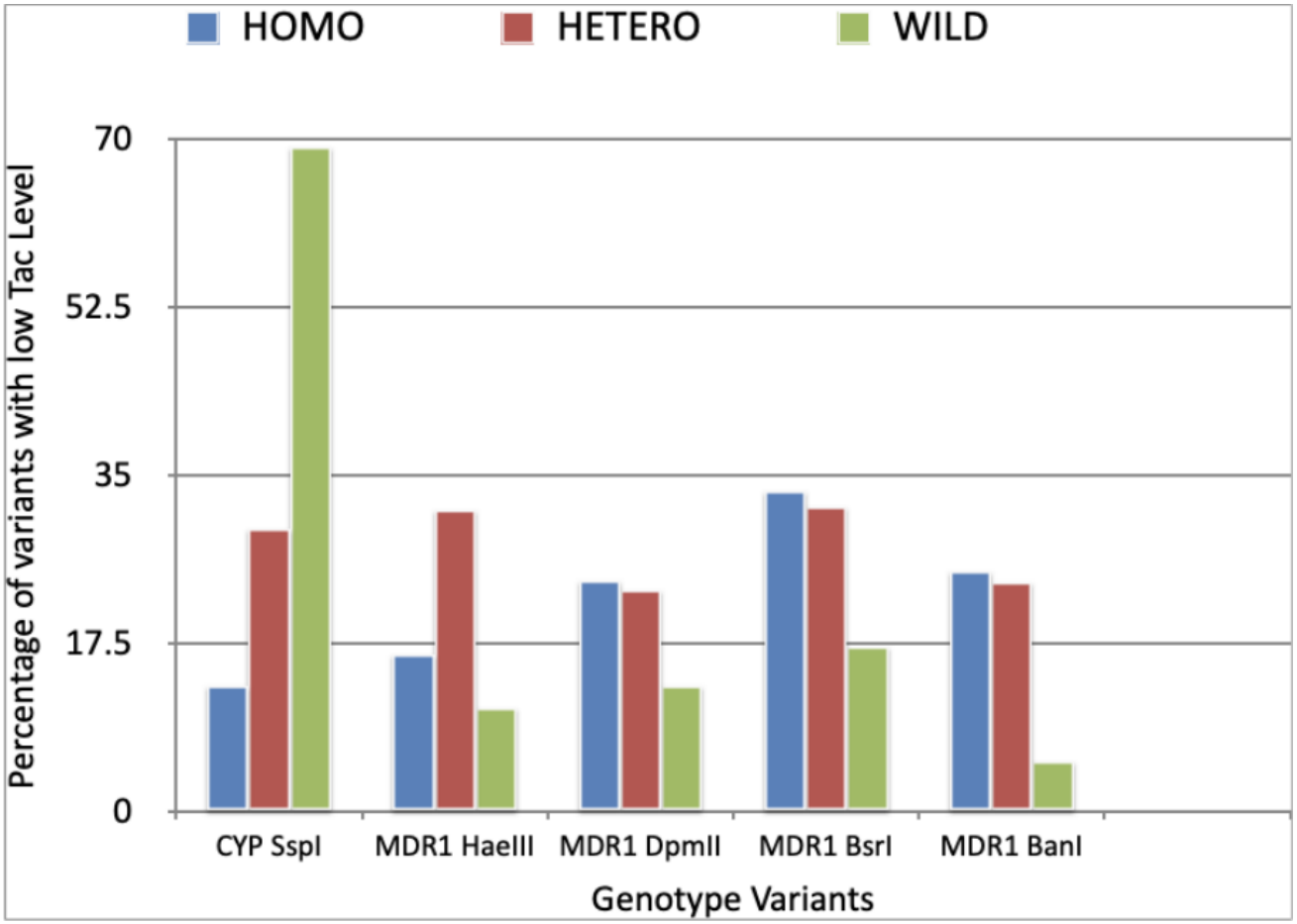

Diagram 3: SNP and Low Tac level

Infections

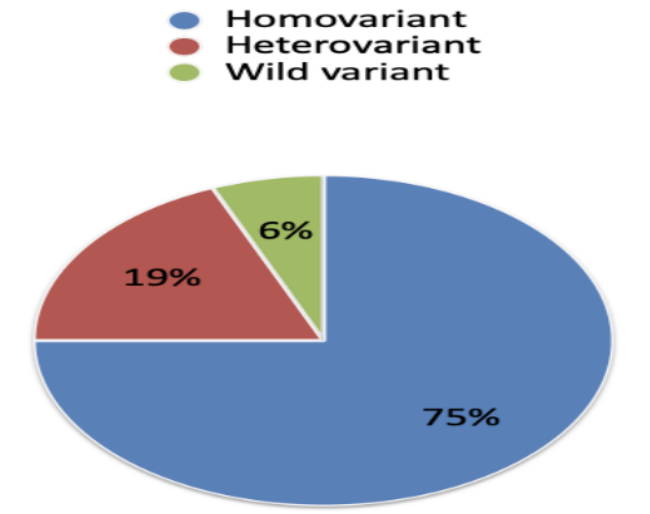

Diagram 4:
Major Infections

Homovariants
Cryptococcal diarrhoea,
Pulmonary Tuberculosis(2),
UTI(3),
Bacteremia,
Esophageal candidiasis(2),
Parvovirus infection,
Pulmonary mucormycosis,
CMV
Heterovarients
Graft Pyelonephritis
Herpes Zoster,
Pulmonary mucormycosis
Wild Variants
Acute Gastroenteritis

Table 2: Major Infections

Results and discussion

1. 69.2% of Wild variants of CYP 3A5 (Fast metabolizers) have low initial tacrolimus levels.
2. 51.5% of Homo variants (Slow metabolizers) have high initial tac levels.
3. However, all variants achieve optimum tacrolimus levels at same time (mean 12.4 days).
4. There were higher number of infections among slow metabolizers.

Conclusion:

1. A fixed dosing regimen with TDM result in high and low initial tacrolimus levels in slow and fast metabolizers respectively
2. More infections in slow metabolizers.
3. Few graft rejections
4. A larger sample with genotype based dosing is required to test such a strategy.