MDR1 genotypes associated with antiviral dynamics and indinavir (IDV) disposition in HIV-infected patients

Peter L. Anderson, Pharm.D.[1], Jatinder Lamba, Ph.D.[2], Erin Schuetz, Ph.D.[2], and Courtney V. Fletcher Pharm.D.[1]

From the Antiviral Pharmacology Laboratory, University of Colorado Health Sciences Center, Denver, CO, USA[1], and St. Jude Children's Research Hospital, Memphis, TN, USA[2].

BACKGROUND: *MDR1* encodes P-glycoprotein , an efflux transporter that protects sensitive tissues including brain, immune cells, and fetuses against substrate xenobioticexposures. P -gp forms a gut barrier against substrate absorption and clears substrates from blood into urine, bile, and intestine. HIV protease inhibitors are P-gpsubstrates in vitro and in animals. Our objective was to characterize the association of MDR1C3435T and G2677T genotypes with IDV disposition and antiviral dynamics. **METHODS:** Antiretroviral naïve adults were participating in a 52 -week study of zidovudine,lamivudine, and IDV. Intensive plasma sampling for IDV was conducted at week 2; concentrations were measured with HPLC/UV. Pharmacokinetics were estimated standard modeling and data inspection. Plasma HIV -RNA was collected monthly; PBMC pellets were stored. All data and PBMC pellets were de -identified and re-coded.Following institutional review board approval, MDR1 genotypes were obtained by PCR/direct sequencing withPolyPhred analysis. Parametric statistics were used for comparisons. **RESULTS:** 33 subjects were genotyped. For the 2677G>T, (Ala893Ser) and 3435C>T respectively, 8 subjects were G G/CC; 4 G/CT; 16 GT/CT; 1 GT/TT; 1 TT/CT; and 3 TT/TT; indicating significant linkage disequilibriumbetween thepolymorphic sites. IDV CL/F (L/H/kg) was lower in the 2677 TT compared with GG groups, 0.48 versus 0.82, respectively (P=0.02), and also in the 3435 TT compared with CC groups, 0.49 versus 0.84, respectively (P=0.04). IDVCmax (µg/mL) was higher in the 2677 TT versus GG group, 10.0 versus 7.2, respectively (P=0.06), and when normalized for dose, 0.93 versus 0.62 per mg/kg/dose (P=0.04). Cmax was not significantly related with C3435T. 2677 TT subjects hada larger decline in log HIV-RNA at week 52 or study exit compared with GT or GG groups, –3.7 versus -3.2 and –2.2 (P=0.008 and 0.04), respectively. Baseline HIV-RNA was marginally higher in the 3435 TT versus CC groups, 5.1 versus 4.4 log copies/mL (P=0.06), but not among 2677 genotypes. **CONCLUSION:** These findings indicate that *MDR1* genotypes influence IDV pharmacokineticsand antiviral dynamics. Other studies have reported conflicting data between MDR1 genotypes and substrate disposition and effects. In this study, *MDR1*2677TT (Ser893) was associated with both higher IDV plasma concentrations and stronger antiviral responses

P-glycoprotein

- P-gp, an ATP-driven drug transporter, likely evolved as a defense against noxious plant and microbial chemicals.
- It has come to light that many drugs including, HIV-1 protease inhibitors are Pgp substrates.
- P-gp's most pronounced effects are to limit intestinal drug absorption, brain penetration, and diffusion across placenta to fetus. [1]

1. Lin. Clinical Pharmacokinetics2003. 42(1) 59-98.

Functional MDR1 allelic variants

- MDR1 encodes P-gp in humans.
- A non -coding C →T mutation at 3435 is associated with reduced P-gp protein in gut.[2]
- 3435 TT homozygoteshad higher digoxin Cmax than 3435 CC homozygotes
- C→T at 3435 is in linkage disequilibrium with G→T at 2677, which encodes Ala893Ser.[3]

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Hypothesis and Objective:

Hypothesis: MDR1 allelic variants associated with lower P-gp expression/functionality will be related with *higher* indinavir concentrations and *stronger* antiviral response.

Objective: Characterize the association of *MDR1* C3435T and G2677T genotypes with IDV disposition and antiviral dynamics in HIV-infected patients.

Methods:

- Antiretroviral adults were participating in a randomized study of concentration-controlled versus standard dosing of ZDV, 3TC, and IDV.
- Subjects were followed monthly. The primary endpoint was 52 weeks. HIV -RNA was obtained on every visit.
- At week 2 of therapy, with standard doses in all patients, an intensive IDV PK study was performed.

Methods:

- After study completion, all data and remaining cell samples were de -identified. IRB exempt approval was obtained for genotyping pharmacology-related loci.
- MDR1 genotypes were obtained by PCR-direct sequencing with PolyPhred analysis.
- Unpaired t-tests were used for comparing data between groups.

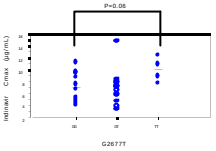
Results:

- Genotypes from 33 patients were obtained.
- Linkage disequilibrium was observed:

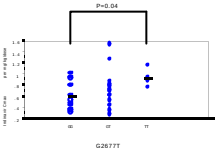
C3435T

G2677T	CC	CT	TT	Totals
GG	8	4	0	12
GT	0	16	1	17
TT	0	1	3	4
Totals	8	21	4	33

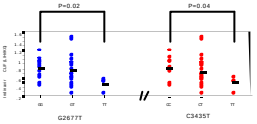
Results: IDV Cmax and G2677T



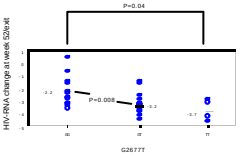
IDV dose -adjusted Cmax



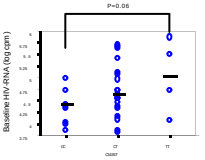
Results: IDV Oral Clearance



Reduction in HIV -RNA at study end



Baseline HIV-RNA



Results:

- The 2677 G allele was more frequent in blacks compared with whites; 6 of 7 blacks and 5 of 23 whites were 2677 GG (Chi-square; P=0.009).
- No significant relationships were found between MDR1 genotypes and CD4 recovery.
- No significant relationships were found between 3435 genotypes and IDV Cmax or antiviral dynamics.

Conclusions:

- MDR1 C→ T 3435 and G→T 2677 were in linkage disequilibrium .
- MDR1 2677TT (Ser893) was associated with reduced IDV oral clearance and a stronger antiviral response.
- Black versus white race and baseline HIV-RNA were related with MDR1 genotypes.

PK/PD of 3435 CC (or 2677 GG)

HIV drug P gp substrate (ref)	Pharmacokinetic effect	Pharmacodynamic effect
IDV (4)	Higher CL/F	Weaker HIV-RNA response
NFV (5)	Higher CL/F	Weaker HIV-RNA response
IDV (6)		Trend stronger immune recovery
NFV/EFV (7)	Lower CL/F (presumably; higher random drug levels)	Weaker immune recovery
IDV or RTV (8)		None Pls (trend stronger immune recovery with NNRTIs)
Unspecified PI (9)	-	Weaker HIV-RNA response
NFV/EFV (10)	-	No immune recovery effects
IDV (11)	Higher 1 hour concentration (AUC not different)	1 hour concentration correlated with glucose disposal

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