EVALUATION OF THE USE OF GENOTYPIC INHIBITORY QUOTIENTS IN AN ANTIRETROVIRAL THERAPEUTIC DRUG MONITORING PROGRAM

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BACKGROUND

- Genotypic inhibitory quotient (GIQ) is a pharmacokinetic / pharmacodynamic (PK/PD) parameter that incorporates viral genotypic resistance data with drug plasma concentrations;
- GIQ = Cmin / # protease mutations present conferring resistance to the protease inhibitor (PI) being measured;
- Relationships between GIQs and virologic response to PI-based antiretroviral (ARV) regimens have been reported for amprenavir (APV), atazanavir (ATZ), lopinavir (LPV), saquinavir (SQV) and tipranavir (TPV);
- The last ARV therapeutic drug monitoring (TDM) guidelines[1] include GIQ cutoff values;
- The Québec Provincial ARV TDM program is operational since June 2006. Our program has access to cumulative genotypic resistance data and uses GIQs (as well as Cmin, concentration ratios and population curves) to interpret PI concentrations.

STUDY OBJECTIVES

- To describe the first GIQ results from the Québec Provincial ARV TDM program;
- To contrast PI TDM interpretations based on target GIQs with those based on target Cmins for PI-experienced patients;
- To describe virologic response following dose adjustments based on GIQ interpretations.

METHODS

- Retrospective review of the Québec Provincial ARV TDM program database;
- Approved by the Director of Professional Services, McGill University Health Centre (MUHC)

Inclusion criteria:

- HIV – 1 infected individuals;
- History of virologic failure to past PI – based regimen, or evidence of primary PI resistance;
- Receiving PI at time of TDM (APV, ATZ, LPV, SQV or TPV);
- Genotypic resistance data available;
- Sample received between June 2006 and end of February 2007 for PI TDM;
- TDM interpretation based on GIQ.

Study Groups

- Group 1: all patients from the cohort meeting the inclusion criteria;
- Group 2: subgroup of group 1, followed at the Montréal Chest Institute with virologic and immunologic data available 0-2 months pre- and 2-3 months post first TDM.

Data collection

Data available from the TDM database include: patient demographics, concomitant medications, indication for TDM, history of PI virologic failure, cumulative protease mutation list (Trugene and/or Virco), ARV measured, dose and concentration (mg/L), and sample time post-dose. Viral load and $CD4^+$ data for group 2 obtained from the MUHC laboratory database.

Pharmacokinetic sampling

- ARV concentrations measured at the Biochemistry Department (MUHC) by a validated and sensitive assay using LC/MS/MS.
- Limits of quantitation (mg/L): APV 0.06, ATZ 0.007, LPV 0.023, SQV 0.008, and TPV 1.49.

TDM interpretations

TDM interpretations based on target Cmins for PI-experienced patients and target GIQs (see table 1). GIQ was calculated by dividing extrapolated Cmin by the number of cumulative protease mutations present as per the mutation score used in the study providing the GIQ target.

Statistical Analysis

- Descriptive statistics; for group 2 Mann-Whitney U test used to compare change in viral load following GIQ-based TDM when TDM advice was followed or not by the treating physician.

Table 1: Target Cmins and GIQs

ARV	Target Cmin PI-experienced (mg/L)	Target GIQ (mg/L)
Amprenavir	1.25[2]	0.75[7]
Atazanavir	0.15[3]	0.1[8]
Lopinavir	5.0[4]	2.1[9]
Saquinavir	0.1[5]	0.35[10]
Tipranavir	20.5[1,6]	13.0[11]

RESULTS

Table 2: Baseline Characteristics of Study Population

Group 1, N=75 (109 TDM interpret.)	
Age (years), mean ± SD	47.0 ± 8.94
Gender, n (%) male	64 (85.3 %)
Protease inhibitor interpreted, n (%)	
- Fosamprenavir / Amprenavir	12 (11 %)
- Atazanavir	22 (20.2 %)
- Lopinavir	57 (52.3 %)
- Saquinavir	10 (9.2 %)
- Tipranavir	8 (7.3 %)
TDM indication, n (%)	
- Virologic failure	37 (33.9 %)
- Control	34 (31.2 %)
- Interaction	25 (22.9 %)
- Other	13 (12.0 %)
Group 2, N=19 (31 TDM interpret.)	
$CD4^+$ (cell/mm^3), mean ± SD	381 ± 325
% undetectable viral load	47 %
If detectable, viral load (log_{10}), mean ± SD	3.46 ± 0.91

Table 3: GIQ results, % subtherapeutic GIQs and Cmins (n=109 interpretations)

ARV	Median # (range) mutations in calculated GIQ	Median (range) GIQ (mg/L)	% subtherapeutic GIQ	% subtherapeutic Cmin
APV	2.5 (1 - 5)	1.07 (0.25-2.8)	41.7	16.7
ATZ	2.5 (1 - 10)	0.20 (0.01-1.75)	22.7	13.6
LPV	3 (1 – 8)	1.5 (0.06-11)	59.6	54.4
SQV	3 (1 - 8)	0.27 (0.02-0.69)	50.0	20.0
TPV	3 (1 – 6)	10.65 (2.3-34)	62.5	25.0

- The percent of discordant TDM interpretations (subtherapeutic, therapeutic, supratherapeutic) based on target GIQs versus target Cmins were:
  APV 25 %, ATZ 18.2 %, LPV 29.8%, SQV 30 %, and TPV 37.5 %;
- 61.9 % of pharmacological advice was followed by the treating physicians;
- 52 % of subsequent GIQ results (2nd and 3rd TDM) were therapeutic.

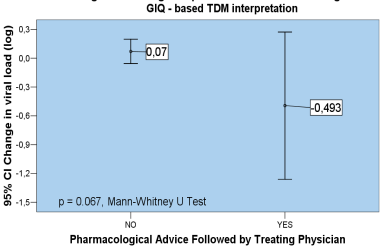
Table 4: % Subtherapeutic GIQs vs Cmins in Group 2, in patients with confirmed virologic failure at baseline, n = 17

Antiretroviral	% subtherapeutic GIQ	% subtherapeutic Cmin
Amprenavir (n=1)	100	100
Lopinavir (n=12)	66.6	41.6
Saquinavir (n=4)	75	50
APV, LPV and SQV (n=17)	70.5	47.1

Table 5: GIQ vs Cmin predictive value of virologic response (Group 2, n = 31 interpretations)

Parameter	GIQ	Cmin
Sensitivity	70.6	47.1
Specificity	63.6	45.5
Positive predictive value	75.0	57.1
Negative predictive value	58.3	35.7

Figure 1: Virologic response 2 to 3 months following first GIQ - based TDM interpretation



CONCLUSIONS

- Virologic response was more closely related to target GIQs than target Cmins for PI-experienced patients;
- GIQ-based TDM interpretations tend to improve virologic response when pharmacological advice is followed by the treating physicians;
- These results must be confirmed with a larger sample size and a longer follow-up period.

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