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

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BACKGROUND

- Genotypic inhibitors (GIQs) are a pharmacokinetic / pharmacodynamic (PK/ PD) parameter that incorporates viral genotypic resistance data with drug plasma concentrations.
- GIQ = Cmin / I protease mutations present when 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 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 Cmins, 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 – 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.

Pharmacokinetic sampling

- ARV concentrations measured at the Biochemistry Department (MUHC) by a validated and sensitive assay using LCM/MS.
- Limits of quantification (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.

RESULTS

- 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

<table>
<thead>
<tr>
<th>ARV</th>
<th>% subtherapeutic GIQ</th>
<th>% subtherapeutic Cmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>APV</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>LPV</td>
<td>66.6</td>
<td>41.6</td>
</tr>
<tr>
<td>SQV</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>TPV</td>
<td>70.5</td>
<td>47.1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GIQ</th>
<th>Cmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>70.6</td>
<td>47.1</td>
</tr>
<tr>
<td>Specificity</td>
<td>63.6</td>
<td>45.5</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>75.0</td>
<td>57.1</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>58.3</td>
<td>35.7</td>
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</table>

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.

ACKNOWLEDGEMENTS

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REFERENCES


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

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

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