Meeting Clinicians’ and Patients’ Needs in the Practice of Therapeutic Monitoring

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Aims

- To increase awareness of the *implementation gap* that affects Pharmacometrics

- To consider current hurdles against rational treatment individualization through monitoring

- To touch on some prospects that might help patients to better benefit from progress in Pharmacometrics
PK Variability of Antiretrovirals: a Deadly Issue

Efavirenz: Still used without Therapeutic Monitoring!

253 unselected patients under Efavirenz 600 mg q.d.:

- BSV = 56%
- IIV = 25%


130 unselected patients under Efavirenz 600 mg q.d.:

- Optimal range
- Viral control
- CNS toxicity

C. Marzolini & al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 2001, 15:71-75
The criterion of Safe and Effective Variability

Standard population or group dosing:

- **Dosage** vs. **Concentration**
- **Target\textsubscript{tox}** vs. **Target\textsubscript{ther}**
- **Target** \( \text{tox} \) and \( \text{ther} \)
- **SEV**
- **PK variability \( \leq \text{SEV} \)**

Therapeutic monitoring / Target control intervention:

- **Dosage** vs. **Concentration**
- **Target\textsubscript{tox}** vs. **Target\textsubscript{ther}**
- **Target** \( \text{tox} \) and \( \text{ther} \)
- **PK variability > SEV**

Holford NH, Buclin T. *Safe and effective variability – a criterion for dose individualization*. Ther Drug Monit. 2012;34:565-8
Voriconazole: Suboptimal exposure in ~50%


Unwilling Drug Companies

- Unlike theranostics, therapeutic monitoring based on either concentrations or biomarkers is badly considered.

- Drug candidates that would heavily rely on monitoring are abandoned (despite provocating examples).

- For other candidates, clinical development resolutely ignores the potential benefits of monitoring.

- Very few incentives come from authorities, prescribers or patients.
Unwilling Prescribers

- The feed-back loop of dosage adjustment is complicated and slow.
- Analytical methods demand large, remote central laboratories.
- Standardized sampling time (usually trough) is a problem.
- Interpretation of concentrations or biomarkers results is uneasy.
- Evidence is scarce regarding actual benefit for patients.
POCT are coming for Therapeutic Monitoring

- **Antibodies:** Surface Plasmon Resonance, Miniaturized Fluorescence Polarization
- **Aptamers:** Remote data collection
- **Microfluidics:** Lab-on-Chip technology
- **Computer-assisted user-friendly interpretation tools:** Connectivity, privacy
- **Central repository for PKPD reference data:** Connectivity, privacy

**Technologies:**
- **Microfluidics**
- **Lab-on-Chip technology**
- **Surface Plasmon Resonance**
- **Miniaturized Fluorescence Polarization**
Dry Blood Spots represent an alternative to minimally invasive sampling. Adjustment instructions and central analysis and interpretation are key components of the process.
Example: Patient receiving imatinib 400 mg/d for chronic myelogenous leukemia. Unsatisfactory response → TDM 920 µg/L 8 h post-dose.
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Is this concentration “normal”? considering drug dosage and patient’s characteristics
Normality or Expectedness relies on Pop-PK

Single study or Systematic Review and Meta-Analysis of studies

Example: Patient receiving imatinib 400 mg/d for chronic myelogenous leukemia. Unsatisfactory response → TDM 920 µg/L 8 h post-dose.

1. Is this concentration “normal”?

2. Is this concentration “good”? for patient’s condition and well-being
Suitability or Appropriateness relies on Pop-PKPD

Single study or Meta-Analysis of studies

Example: Patient receiving imatinib 400 mg/d for chronic myelogenous leukemia. Unsatisfactory response → TDM 920 µg/L 8 h post-dose.

1. Is this concentration “normal”?
2. Is this concentration “good”?
3. How to reach optimal exposure? through dosage and follow up decisions

Prediction percentiles:
- P90
- P75
- P50
- P25
- P10

Therapeutic target: 1000 µg/L (750-1500)

Dose adjustment: Therapeutic target: 1000 µg/L (750-1500)

Imatinib (ng/mL)

6:00 12:00 18:00 24:00 6:00

400 mg

920 µg/L

975 µg/L

650 µg/L
Decision Support relies on Bayesian Adaptation

Computer tools have been made available!

BestDose  MWPharm  Simulo

InsightRx  Dose-Me  Tucuxi  etc.
Evidence remains largely to be produced

Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial

V Gotta, N Widmer, L-A Decoster, Y Chalandon, D Holm, M Gregor, R Beni, L Leondit-Francois, G M Baerlocher, M.A. Duchosal, C Cojak, T Buclin

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Abstract

Purpose This study assessed whether a cycle of “routine” therapeutic drug monitoring (TDM) for imatinib dosage individualization, targeting an imatinib trough plasma concentration (Cmin) of 1,000 ng/ml (tolerance: 750-1,500 ng/ml), could improve clinical outcomes in chronic myelogenous leukemia (CML) patients, compared with TDM use only in cases of problems (“rescue” TDM).

Methods Imatinib concentration monitoring evaluation was a multicenter randomized controlled trial including adult patients in chronic or accelerated phase CML receiving imatinib since less than 5 years. Patients were allocated 1:1 to “routine TDM” or “rescue TDM”. The primary endpoint was a combined outcome (failure- and toxicity-free survival with continuation on imatinib) over 1-year follow-up, analyzed in intention-to-treat (ISRCTN1182395).

Results Among 56 patients (55 evaluable), 14 (52%) receiving “routine TDM” remained event-free versus 13 (57%) “rescue TDM” controls (p = 0.69). In the “routine TDM” arm, dosage recommendations were correctly adopted in 14 patients (median Cmin: 895 ng/ml), who had fewer unfavorable events (25%) than the 13 not receiving the advised dosage (77%; p = 0.03; median Cmin: 648 ng/ml).

Conclusions This first target concentration intervention trial could not formally demonstrate a benefit of “routine TDM” because of small patient number and surprisingly limited prescriber’s adherence to dosage recommendations.


56 CML patients treated < 5 years
1:1 Randomization
No difference
28 patients offered routine TDM
Recommendation
14 CORRECTLY FOLLOWED
13 POORLY OR NOT APPLIED
1 lost to follow up

28% rescue TDM
77%
p=0.03
### Small molecule STIs now approved by EMA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Company</th>
<th>EMA</th>
<th>Indications</th>
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Authorities are to Convert!

Exposure-Response Analysis in Drug Development and Regulatory Decision Making

FDA recently announced a public docket entitled “Exposure-Response Analysis in Drug Development and Regulatory Decision Making; Request for Comments” (https://go.usa.gov/xOamz) to give interested parties a opportunity to identify areas of scientific policy that may need further clarity or elaboration, as well as any obstacles preventing use of exposure-response analyses in drug development and regulatory review.

Please go and fill in the ISoP Response Form to insist on the importance of assessing PKPD variability and of systematically evaluating the potential merits of therapeutic monitoring, based on either concentrations or biomarkers!
Conclusions

- Pharmacometrics bring about key components for the advocated precision medicine
- Technological advances will shape and foster new forms of therapeutic monitoring
- Pharmacometrists have a definite responsibility in bridging the implementation gap