

Post-Budapest

PK & PD of Existing and New
Drugs

Marie Courchesne

Introduction

- 27 presentations in 1 day
as abstracts/posters highlights

Topics of Discussion

- Review main key presentations/poster sessions of 2nd day of meeting
- Highlights practical issues

J. Currier on Women's health issues

- UNAIDS 2006: 50% ♀
- ↑↑ each year
- Natural Hx : lower viral load at detection
- Little evidence of slower progression
- Earlier ↓↓ survival \propto access to Tx
- HAART Response: Only cohort studies

Gender differences PK/PD

- Estrogen: slows down gastric emptying
- Higher drug levels for all classes of ARVS
- Higher triphosphates
- ? Difference in density of CCR5
- Reduced expression of PgP

Toxicities

- Lactic acidosis: 85% ♀
- NNRTI rash: 9.5% ♀ / 1.1%

Conclusions

- Overall no sex difference to TX
- Less is known about tolerability
- Pre-planned analysis integrated into clinical trials required.

LPV PK in pregnancy L. Else Liverpool #10

- ↑↑ G-I transit time
- ↑↑ Plasma
- Peytavin showed significant ↓↓
LPV C min in T2 T3

Foetus exposure

- Measured as Cord/Mother ratio of unbound = pharmacologically active
- LPV: bound to α 1 acid glycoprotein
- ↓aag in T3 vs T2
- Placental transfer of LPV limited with a mean ratio C/M 0.17

EFV in Children

D Burger #51

- Initial dose of 11.7mg/kg
- Followed dosing table in monograph: unvalidated
- Mixed naïve and experienced 33 patients > 3 y old

EFV results

- Linear correlation EFV clearance vs age
- No significant trends towards AE related to toxic levels
- 80% therapeutic levels

Analysis

- More variability in younger
- ? Effect of 2B6 expressions lower in infants but higher 6m-3y
- Non-adherence vs low level
may be interpreted like higher clearance rate

PK of TNF and ATV/RTV

Jennifer Kiser #12

- Hypothesis: Young adults: faster clearance of ATV and TNF
- ↑↑ Doses based on BMI
- + Bi directional interaction ATV
25%↓ AUC and TNF ↑ 37%
(Taburet)

22 patients (9 female)

- ATV /RTV with light fat meal 400-500 cal
analysis at 1 –2
4-6-8-12-24h
non compartment
analysis

ATV:AUCge m
36mcg*hr/ml
C max 3504ng/ml
C 24 578ng/ml

- TNF mean
- AUC 2.8mcg*hr/ml
C max 254 ng/ml
C 24 60 ng/ml

Conclusions

- ATV 10% increase clearance with 10 kg increase
- TNF 6.8% increase clearance with 10 kg increase

Forgiveness of SAQ die #14

- Fn: robustness of TX
- No inducer/inhibitor
- 77 profiles
- Saq HG100/100 bid
- Saq HG1600/100 qd
- Saq HG2000/100 qd

Analysis of 10th percentile curve <
MEC=100ng/ml

1000	1600	2000
0.5 h	9 h	8.4 h

- 1000/100 bid >
 - 2000/100 qd >
 - 1600/100 qd
- due to low RTV

Higher C trough
and t_{1/2} in
intracellular/
plasma

No definition of PK
for QD

Palatability of invirase opened caps /RTV

- At request of FDA
- Suspended in food
- Simple syrup> jelly jam>
unopened>babyformula
- But no difference in exposure

PK of ABC and its anabolite Carbovir TP M Boffito

- Patients switched from ABC bid to die
- 34 patients: 29 completed

Results

- Mean concentration Vs time
- CBV TP C trough 300 bid
= 600 die but AUC & C max higher
ABC AUC similar
- CBVTP AUC 2.09 fold > women/men
- ABC AUC 38% women > men
- Difference in transporter may explain higher transformation

Caution: assays may differ

Integrase inhibitors

D Házuda

- Selectively inhibits strand transfer
- Binds divalent metals in active site
- High affinity binding to complex(viral) DNA competing with host cell
- Products are highly protein bound which may lead to hypersens.

Mean effect on MK 0518

	C12	AUC	C max
ATV/RTV	77%↑	41%	24%
TPV/RTV	55%↓	24%	18%
Rifampin	61%↓	40%	38%
EFV	21%↓	36%	

Raltegravir

- Enhanced efficacy in macrophages
And penetration in reservoirs
- Metabolized by glucuronidation
- 400 mg bid
- Cross resistance to GS9137
- Response 10 days

Maraviroc PK

P Chan # 16

- Reversible selective CCR5
- CYP 3A4 subst.
- 2 compartment 1st order absorption with lag time
- Non linear PK
- Boosted with RTV
- Higher C_{min} at wk 2= greater VL drop but not persisting beyond wk 16
- Asian 17.7% higher bioavailability and lower extraction
- Food lowers bioavailability and dose dependant resposne

HAART with TB

A Pozniak

- < 100 CD4 ASAP
- 100-200 after 2m
- >200 TB 1st
- Watch for IRIS 1-7%
- Rapidly increasing CD4
- Related to HAART
- High fever

Rifampin

- Induction lasts 10-14 days
- Delay dose readjustment when DC TB RX
- With EFV or NVP
- Dose readjustment may not be necessary
- Avoid boosted PI
- LPV : LFT↑=DC
- SAQ1000/100RT bid= LFT 20x

Rifabutin

- With LPV/RTV if RFB 3x/week
? Efficacy of RFB

SAQ 800/600–IDV400/r100 bid in Thailand

T. Cressey # 31

- Adequate trough > 100 ng/ml in 23/24 or 16/17 subjects
Main AE TG↑ requiring dose reduction or LFT↑
- Transitional option until new med available

PF 00821385

J Davis # 17

- Oral gp120 inhibitor
- Inhibits interaction of GP 120 with CD4 by binding to GP 120
- Activity against CxCR4 and 5 of clade B
- Rapid absorption fasted
- Predicted dose required 70% higher than tolerated

Rifampin and CYP4502B6 genotype K Cohen #31

- CYP2B6 G516T polymorphism ↑↑
[EFV] sp in Afr
- EFV not increased while on TB
RX
- No difference on median with/wo
RFP
- 17 own control: no difference
- G516T strongly associated with
>4mg/L

PK of reduced dose of stavudine G Peytavin #33

- Purpose: better neurological status
- 30mg for > 60 kg
- Results: maintain VL control
- Increase in mt DNA in 62% patients
- Significant decrease in Total Cholesterol, HDL and ALT at w24 and 48

Tipranavir PK , liver fibrosis and toxicity

J Morello #35

- 29 patients on TPV/RTV
- 7/29 co infected with C
- Significant liver fibrosis in 7/29
- Positive correlation TPV level and fibrosis as well as AST or ALT at baseline and w12
- Mean 58mcg/ml vs 28
- Level in HCV >uninfected not significant

ATV PK D Burger #36

- No significant C min and Virological response w/o mutations but Cmin relation to total bilirubin
- Significant GIQ and response with mutations
- $GIQ > 0.23\text{mg/L/mutation}$ only 11% failure

Kaletra PK variability

S Gibbons # 37

- Retrospective audit Kaletra 400/100 bid trough levels
- Use of TNF or RFB noted
- Age and TNF: no correlation
- Weight : inverse correlation
- RFB : Median increase of LPV 5176 to 9364 ng/ml

Kaletra trough vs V L

Y Chiu

- In naïve patients
 - lack of association between trough and virological response
 - analysis with logistic regression
 - modeling of 4 previous studies

Use of GIQ in TDM

N Sheehan

- GIQ showed better sensitivity(70.6%)
- Specificity (63.6%)
- Positive predictive value (75%)
than targeted concentrations
Pharmacological advice followed
mean decrease of 0.49 copies/ml