Impact of Antiretroviral Therapy (ART), Immunosuppression and Viraemia on Lipid Levels: The D:A:D Study

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Abstract P034

Aims/Methods

- **Aims of the study**: To investigate the impact of ART, HIV viraemia and immunosuppression on triglyceride (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) levels

- **Methods**
  - First available TG, TC and HDL-C (mmol/L) on/after enrolment in D:A:D Study was considered, with TG log10 transformed to ensure Normality
  - Associations between each lipid level and ART use, HIV viral load (VL), and CD4 count were examined using linear regression
  - Models included adjustment for: Age, Gender, Mode of infection, Ethnicity, Prior AIDS, Body mass index (BMI), Smoking, Family history of CVD, Diabetes, Use of lipid lowering drugs, Hepatitis-C co-infection, Cohort, Year of D:A:D entry
Impact of ART, Viraemia and Immunosuppression on TC

Figure 1a: Impact of ART and latest VL on TC

Figure 1b: Impact of immunosuppression on TC


Impact of ART, Viraemia and Immunosuppression on TG and HDL-C

• Lower TG levels (N=44 322) were seen amongst those:
  – Off ART (compared to those on ART with suppressed VL)
  – With lower current CD4 count
  – Higher TG levels were seen amongst those with lower nadir CD4 count

• Lower HDL-C levels (N=38 604) were seen amongst those:
  – Off ART (compared to those on ART with suppressed VL)
  – On ART with VL>500 copies/ml (compared to those on ART with suppressed VL)
  – With a lower current CD4 count
  – With a lower nadir CD4 count

Advanced Chronic Kidney Disease, End-Stage Renal Disease and Renal Death in HIV-positive individuals in Europe

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Abstract O314

Methods

• Follow-up from first eGFR measurement >1/1/2004 to last eGFR or Adv CKD/ESRD/Renal Death, whichever occurred first
  – Prevalent Adv CKD/ESRD led to exclusion

• eGFR calculated with Cockcroft-Gault

• Poisson Regression Models adjusted for
  – Demographic factors (ethnicity, gender, age)
  – Traditional renal risk factors (baseline eGFR, prior CV event, diabetes or hypertension)
  – HIV-related factors (current/nadir CD4 count, VL, HCV/HBV and prior AIDS)

• Kaplan-Meier method used to estimate time to events and outcome following Adv CKD/ESRD

**Study Design**

**EuroSIDA**

N=16,597

>1 eGFR > 1/1/04
N=10,038

> 3 eGFRs
N=8,831

Baseline eGFR> 30 & no ESRD N=8,817

- No Adv CKD/ESRD N=8,772 (99.5%)
- Renal event N=45 (0.5%)
- Renal death (N=2)
- Adv CKD (N=24)
- ESRD (N=19)

Median Follow-up 4.5 yrs (IQR 2.7-6.8) and 37,056 PYFU
Incidence Rate 1.21/1000 PYFU (95%CI 0.86-1.57)


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**Kaplan-Meier Progression to Adv CKD/ESRD/Renal Death**

- Either event
- Adv CKD
- ESRD/Renal Death

Percentage with Adv CKD/ESRD/Renal Death

N 8817 8553 7585 6164 4960 3522 1850

Months After Baseline

Predictors in Uni- & Multivariate Analyses

Baseline eGFR (per 10 ml/min higher) $P<0.0001$
Baseline Age (per 10 yrs older) $P=0.10$
CD4 (per 2-fold higher) $P=0.029$
Cardiovascular risk (any risk vs low risk) $P=0.0095$
HCV (HCV-ab pos vs neg) $P=0.35$
Prior AIDS (yes vs no) $P=0.76$

Underlying Causes of Deaths After Adv CKD/ESRD

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Absolute Number of Deceased Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td>Malignancies</td>
<td>2</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
</tr>
<tr>
<td>CVD</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>1</td>
</tr>
<tr>
<td>COPD</td>
<td>1</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
</tr>
</tbody>
</table>

Limitations

• Infrequent events
• Competing risks
• eGFR availability - Adv CKD underascertainment
• Case definition
• No proteinuria or other urinary markers
• Results may not be generalisable to non-Caucasian populations or those in treatment-limited settings

Summary and Conclusions

• Adv CKD/ESRD/Renal Death incidence in EuroSIDA was low (1.2/1000 PYFU) during 4.5 years median follow-up
• Most cases had pre-existing renal impairment, but few experienced rapid progression from normal eGFR levels
• Independent predictors: baseline eGFR, CD4 count and any cardiovascular risk
• Underpowered to assess relation to individual ARVs such analyses are ongoing in the D:A:D study
• Outcome after Adv CKD/ESRD was poor with >20% estimated to have died within 12 months
The effect of zinc sulphate supplementation on atazanavir/ritonavir associated hyperbilirubinemia

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INTRODUCTION

- Atazanavir inhibits UGT1A1, a hepatic glucuronotransferase enzyme responsible for the metabolism of bilirubin (from insoluble unconjugated bilirubin to soluble conjugated bilirubin).
- Inhibition of UGT1A1 results in an increase in unconjugated bilirubin levels in blood, leading to an indirect hyperbilirubinemia (HBR).
- Gilbert’s syndrome is a hereditary metabolic condition caused by a UGT1A1 mutation; as a result bilirubin is not efficiently conjugated in the liver and unconjugated bilirubin accumulates in blood.

- Individuals with Gilbert’s syndrome are usually homozygous for the UGT mutation (5-10% of Caucasians) although heterozygotes also have elevated serum bilirubin levels compared to those with no mutation. Individuals with Gilbert’s syndrome are > 9 times more likely to discontinue atazanavir for HBR [1].
- Zinc sulphate (ZnSO4) administered at a dose of 40-100mg inhibits enterohepatic cycling of unconjugated bilirubin and was shown to reduce serum levels of unconjugated bilirubin in persons with Gilbert’s syndrome, both acutely (after one dose) and chronically (after 7 days of dosing) [2]. This supports the potential value of ZnSO4 supplementation in the management of unconjugated HBR.
- We are here investigating whether zinc sulphate administration is effective in lowering blood concentrations of bilirubin in patients with HBR secondary to atazanavir/ritonavir intake.

OBJECTIVES

Primary

- To assess the change in unconjugated HBR following acute and chronic administration of ZnSO4 during atazanavir/ritonavir therapy.

Secondary

- To assess the safety and tolerability of ZnSO4 supplement when given concomitantly with atazanavir/ritonavir.
- To assess atazanavir plasma exposure in the presence of ZnSO4.

METHODS

- This was an open label, two phase, randomised, pharmacokinetic study carried out in HIV-infected patients currently attending for care at the St. Stephen’s Centre, Chelsea and Westminster Hospital, London.
- Patients with total bilirubin concentrations > 25 μmol/L, a viral load < 40 copies/mL, and stable on antiretroviral therapy comprising of Truvada and atazanavir/ritonavir were enrolled.
- Randomisation was performed at baseline (1:1) into either Arm A or Arm B. Atazanavir, ritonavir and total bilirubin and conjugated bilirubin concentrations were measured over 24 hours:
  - following drug intake (without ZnSO4, day 1 for all patients)
  - following a single dose of ZnSO4 (day 2 [Arm A] or day 15 [Arm B])
  - following 14 days of ZnSO4 administration multiple dose (day 15 [Arm A] or day 28 [Arm B]).
- Pharmacokinetic parameters of both bilirubin and atazanavir were calculated using non-compartmental modelling (WinNonlin®) and expressed as median and range. Within-patient changes in pharmacokinetic parameters were evaluated by calculating geometric mean ratios (GMR) and 90% confidence intervals (C.I.; Day 1 as reference) determined using logs of the individual geometric means and expressed as linear values.

RESULTS

- 16 male patients completed the study maintaining virologic suppression throughout.
- ZnSO4 was well tolerated and no grade 3 / 4 adverse events were observed.
- We observed a decline in total bilirubin Cmax in both single and multiple ZnSO4 intake compared to reference phase (Table 1).
- No significant changes in conjugated bilirubin were observed, indicating that the changes were secondary to declines in the unconjugated fraction.
- Atazanavir pharmacokinetic parameters and GMR (90% CI) for Cmax in ZnSO4 and atazanavir, after single and multiple dose of ZnSO4, are illustrated in Table 3.
- All individuals with the exception of one (whose levels were low throughout the study) maintained atazanavir concentration above the suggested MEC of 150 ng/mL.

CONCLUSIONS

- The intake of ZnSO4 led to a moderate decrease in total bilirubin Cmax and overall exposure.
- However, a decrease in atazanavir concentrations was also observed. In this short term study, it did not affect virological response.
- Further data are required to understand whether ZnSO4 supplementation could represent a useful tool in the management of atazanavir related HBR.

Table 1. Pharmacokinetic parameters for plasma total bilirubin (μmol/L)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C0 (μmol/L)</th>
<th>Cmax (μmol/L)</th>
<th>AUC24 (μmol/L·h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study phase</td>
<td>No ZnSO4</td>
<td>Single dose</td>
<td>Multiple dose</td>
</tr>
<tr>
<td>Median (range)</td>
<td>33 (14-63)</td>
<td>32 (7-45)</td>
<td>27 (12-52)</td>
</tr>
<tr>
<td>GMR (90% CI)</td>
<td>0.85 (0.71 - 1.02)</td>
<td>0.84 (0.70 - 1.00)</td>
<td>0.94 (0.77 - 1.10)</td>
</tr>
</tbody>
</table>

Table 2. Pharmacokinetic parameters for plasma unconjugated bilirubin levels (μmol/L)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C0 (μmol/L)</th>
<th>Cmax (μmol/L)</th>
<th>AUC24 (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study phase</td>
<td>No ZnSO4</td>
<td>Single dose</td>
<td>Multiple dose</td>
</tr>
<tr>
<td>Median (range)</td>
<td>26 (12-59)</td>
<td>24.5 (11-36)</td>
<td>20 (3-32)</td>
</tr>
<tr>
<td>GMR (90% CI)</td>
<td>0.76 (0.55 - 1.04)</td>
<td>0.74 (0.54 - 0.91)</td>
<td>0.83 (0.65 - 1.02)</td>
</tr>
</tbody>
</table>

Table 3. Pharmacokinetic parameters for plasma atazanavir concentrations (ng/mL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-24 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study phase</td>
<td>No ZnSO4</td>
<td>Single dose</td>
</tr>
<tr>
<td>Median (range)</td>
<td>24.5 (11-1691)</td>
<td>491 (133-839)</td>
</tr>
<tr>
<td>GMR (90% CI)</td>
<td>0.91 (0.67 - 1.16)</td>
<td>0.92 (0.58 - 0.91)</td>
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</table>