EDCTP funded PhD project Progress report

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Anti tubercular-anti retroviral drugs induced hepatotoxicity and interaction of these drugs at the level of CYP 450 metabolism

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Introduction

- TB is one of the leading causes of morbidity and mortality in the world
- Each year approximately nine million people acquire MTB infection, and three million people die of it
- HIV infection increases risk of TB
- HIV positivity in TB patients $\approx$ 70% in sub-Saharan Africa

Introduction (…cont'd)

- Ethiopia ranks 8th from the 22 high burden countries with an incidence rate of all cases of TB=> 353/100,000 (2006)

- In Ethiopia TB/HIV ranges => 6.6% to 58% (1990-2006)

Introduction (…cont'd)

- DOTS coverage in Ethiopia is 70%
- Although effective therapy is available for both TB and HIV, there are major problems in the concurrent treatment of TB and HIV

Introduction (…cont'd)

- **Challenges** of **HIV and TB Co-infection**

1. High pill burden

2. Adherence issues

3. Paradoxical immune reconstitution reactions

4. Overlapping drug toxicities

5. Drug-drug interactions

Introduction (…cont'd)

Adverse drug reactions

- Few published data on safety profile
- ≈ 25% of patients taking both HAART and anti-TB discontinued treatment
- Most common ADR is DIH

Introduction (…cont'd)

Drug-drug interaction

- Reduction in plasma concentration of PIs and NNRTIs by rifamycins

- RMP reduces the AUC of EFV by 22–26% and NVP by 31%

=> treatment failure and emergence of drug resistance

Introduction (…cont'd)

- Interaction is between INH and ARVs
- *In vitro* studies => INH inhibits the activity of CYP 450 3A4 and 2C19 in human liver
- But have not been adequately studied

Significance of the study

- Prevalence of hepatotoxicity and identification of risk factors for DIH in an Ethiopian setup

- Drug-drug interaction profile in patients taking anti-TB and ARV concomitantly

- See the genetic profile of the different drug metabolizing enzyme in Ethiopians

So,

Phase I

Objectives

- GENERAL OBJECTIVE

  Assess and compare the prevalence , severity and prognosis of hepatitis induced by first-line anti-TB drugs in Ethiopian HIV + ve & - ve patients and identify associated risk factors

Methods cont.

- Inclusion criteria

1. Age > 18 years of both sexes
2. Clinically and / or Laboratory confirmed patients with TB
3. All patients who signed for the informed written consent

Methods cont.

- Exclusion Criteria

1. Patients with known active or chronic active liver disease in whom avoidance of hepatotoxic anti-TB drugs is indicated
2. Patients with base line Liver function test above normal
3. Previous or ongoing treatment with anti TB
4. Pregnancy

Methods Cont.

- Sample size: 103 HIV +ve and 94 HIV -ve
- Data Collection and Analysis

⇒HIV screening

⇒Consent

⇒Relevant demographic , clinical and lab data including NAT-2 determination

⇒Patient follow up

⇒SPSS Version 11.0

Definition of DIH

- Hepatotoxicity will be diagnosed based on a standardized toxicity grade scale which classified severity based on changes of the serum AST or ALT levels relative to the upper limit of normal (ULN):

  – Grade 1 (>ULN-2.5 X ULN)
  – grade 2 (>2.5–5.0 X ULN)
  – grade 3 (>5.0– 20.0 X ULN)
  – grade 4 (>20.0 X ULN)

Results and Discussions

TABLE 1. FREQUENCY DISTRIBUTION OF DEMOGRAPHIC VARIABLES FROM NEWLY DIAGNOSED TB PATIENTS FROM ST. PETER'S TB SPECIALIZED HOSPITAL ETHIOPIA

Variables	Status	Number of patients	Percentage
Age	<35	131	67.2
	≥35	64	32.8
Sex	Male	105	53.3
	Female	92	46.7
BMI	<18.5	108	58.7
	18.5-24.9	71	38.6
	25-29.9	5	2.7
History of Jaundice	Yes	14	7.2
	No	180	92.8
History of blood transfusion	Yes	5	2.6
	No	191	97.4
History of chronic illness	Yes	5	2.6
	No	191	97.4
Traditional medicine intake	Yes	35	18.2
	No	157	81.8
Alcohol intake	Yes	74	38.1
	No	120	61.9

Results & Discussions Contd.

TABLE 2. FREQUENCY DISTRIBUTION OF CLINICAL VARIABLES FROM NEWLY DIAGNOSED TB PATIENTS FROM ST. PETER'S TB SPECIALIZED HOSPITAL ETHIOPIA

Variables	Status	Number of patents	Percentage
HIV status	Positive	103	52.3
	Negative	94	47.7
Type of TB	Pulmonary	146	74.9
	Extra pulmonary	32	16.4
	Disseminated	17	8.7
Anti-TB drugs	SRHZ	142	72.4
	ERHZ	10	5.1
	RHZ	44	22.5
Concomitant drug intake	Yes	55	28.5
	No	138	71.5
HBsAg	Positive	14	7.2
	Negetive	181	92.8
Anti-HCV Ab	Positive	4	2.2
	Negative	177	97.8
CD4 count/mm^3	0-50	15	17.2
	51-100	32	36.8
	101-200	22	25.3
	>200	18	20.7

Table 6 . Association between Biochemical Hepatotoxicity with different clinical variables

Variable	Status	OR (95% CI)
HIV status	Positive	3.6 (1.5-8.5)
	Negative	1.0
Concomitant drug intake	Yes	2.7 (1.2-5.8)
	No	1.0
CD4 count/mm3	0-50	20.5 (2.1-195.6)
	51-100	5.9 (0.6-52.2)
	101-200	4.2 (0.4-41.7)
	>200	1.0

Results & Discussions contd.

- The prevalence of biochemical DIH is 17.3% and clinical DIH is 4.1%
- Biochemical DIH is higher in females and a statistically significant association was seen between being female and clinical DIH
- Age and DIH
- Malnutrition and DIH
- HIV and CD4 count with DIH

Results & Discussions contd.

- Concomitant Drug intake and DIH
- HCV and HBV with DIH
- Death and DIH
- NAT-2 Genotype and DIH
- Slow/Rapid acetylators = 53.6% / 46.4%

Phase II

Project 1

• Comparison of DIH in HIV positive TB patients taking anti-TB and ARV concomitantly and in patients taking anti-TB alone

Aim

• To assess and compare the prevalence, severity and prognosis of DIH in HIV positive patients taking anti-TB and ARV drugs concomitantly and those taking anti-TB alone

Project 2

- **Distribution of CYP 450 3A4, 3A5, 2C9/19, 2B6, NAT2 polymorphism and association between polymorphism of these genes and DIH**

Aim

- **To do genotyping of CYP 3A4, 3A5, 2C9/19, 2B6, NAT2 and to evaluate the association between polymorphism of these genes and DIH in newly diagnosed smear positive TB patients from Ethiopia**

Project 1 & 2

Method:

- 134 newly diagnosed smear positive TB/HIV co-infected patients in Addis Ababa, Ethiopia will be enrolled

- Determination of CYP 450 3A4, 3A5, 2C9/19, 2B6, NAT2 polymorphism will be done by PCR RFLP and allele-specific PCR for genotyping

- Patients will be followed for development of DIH for 2 months

Methods (…cont'd) for project 1 & 2

- Study period: August 2006-Aug 2009
- Diagnosis and treatment of TB/HIV will be according to the Ethiopian National guidelines
- **Attended relevant courses and training**
- Ethical approval => obtained
- DNA extraction => Ethiopia
- Genotyping=>Karolinska Institutet, Sweden

Progress on the project cont.

- 250patients were screened
- 26 patients enrolled
- Reasons for the large gap between pts screened and enrolled were being
  - HIV negative
  - Extra pulmonary TB with no FNA or biopsy confirmation
  - Already on ART
  - Previous anti TB treatment
  - High CD4 count
  - Refusal of PIHCT
  - Residing outside Addis Ababa

- 2 patients developed hepatotoxicity
- 1 Developed clinical DIH and was managed by discontinuation of his anti TB with a stepwise escalation afterwards

Challenges

- Low enrollment rate
  - Other similar studies being conducted in Addis Ababa
  - Very tight inclusion criteria
- Lengthy ethical approval process

Credits

- EDCTP

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