Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet

INCIDENCE, PREDICTORS AND BIOMARKERS FOR ANTIRETROVIRAL AND/OR ANTI-TUBERCULOSIS DRUGS INDUCED LIVER INJURY

Academic Thesis

The public defence for the degree of Doctor of Philosophy at Karolinska Institutet will be held at Karolinska Institutet, Alfred Nobel Allé 8, Floor 6, room 6F, Karolinska University Hospital, Huddinge.

27th January, 2012: 09:30

By: Getnet Yimer Ali, MD, MSc

Main Supervisor:
Assoc. Professor Eleni Aklillu,
Karolinska Institutet

Co-Supervisors:
Professor Lars Lindquist
Karolinska Institutet

Professor Eyasu Makonnen
Addis Ababa University

Professor Getachew Aderaye
Addis Ababa University

Faculty opponent:
Professor Ian Cotgreave
Karolinska Institutet, Institute of Enviromental Medicine and Astra Zaneca, Sweden

Examination board:
Professor Hans Glaumann
Karolinska Institutet,
Department of Pathology

Professor Hanns-Ulrich Marshall
University of Gothenburg
The Sahlgrenska Academy Institute of Medicine, Department of Internal Medicine

Assoc. Prof. Mia Wadelius
Uppsala University,
Department of Medical Sciences

Stockholm 2012

Abstract

Anti-tuberculosis and/or antiretroviral drugs induced liver injury (DILI) is a major challenge when managing TB and/or HIV patients. The aims of this thesis were to identify incidence, risk factors, and management of DILI among 4 different treatment groups namely; HIV positive individuals with no TB co-infection and had a CD4 count of < 200 cells/µl (taking ARV drugs alone = arm 1), TB-HIV co-infected patients with a CD4 count of < 200 cells/µl (taking both anti-TB and ARV drugs = arm 2), TB-HIV co-infected patients with a CD4 count of > 200 cells/µl (taking anti-TB alone = arm 3), HIV negative TB patients (taking anti-TB alone = arm 4).

Newly diagnosed TB and/or HIV patients were prospectively followed for 56-weeks after initiation of anti-TB and/or ARV treatment. All patients were evaluated clinically and biochemically for development of DILI in each visit. Laboratory tests performed include; hepatitis B surface antigen and anti-hepatitis C virus antibody. Liver enzymes and function tests were measured before and during therapy. Associations of DILI with CYP2B6, CYP3A5, NAT2 and UGT2B7, ABCB1, SLCO1B1 genotypes as well as plasma efavirenz and 8-hydroxyefavirenz concentrations were evaluated.

In the pilot study which involved HIV positive and negative TB patients (n=197), who were taking anti-TB alone, the incidence of DILI was 17.3%. DILI was noted to have a statistically significant association with having a lower CD4 count and concomitant drug intake.

The main study, which involved the 4 different arms (n=953) showed that incidence of DILI was still high and significantly associated *with the specific arm the patient belonged to*. The highest incidence was observed in arm-2 (23.5%) >arm-3 (11.6%) >arm-1 (8.1%) >arm-4 (2.8%). DILI was significantly associated with lower baseline platelet, albumin, and CD4 count. Moreover, higher plasma viral load, EFV level, baseline ALT, AST, ALP, and CYP2B6*6 were also good predictors for development of DILI among arm 1 patients. Similarly, a statistically significant association between DILI and female sex, higher plasma efavirenz level, efavirenz/8-hydroxyefavirenz ratio, baseline AST, ALT, lower haemoglobin, and serum albumin was observed among participants in arm 2. NAT2 slow-acetylator, CYP2B6*6/*6, and ABCB1 3435TT genotype were also seen to contribute for development of DILI in arm 2 patients. The median time for development of DILI was 1-2 weeks after initiation of treatment, depending on the arm, with the majority developing it in the first 8 weeks.

In conclusion anti-TB and/or ARV DILI is found to be a major problem among TB and/or HIV patients in Ethiopia. Hence, regular monitoring of liver enzymes during early therapy is recommended for better management. Particularly among those with an underlying risk factors; female, concurrent anti-TB and ART, advance HIV disease, elevated liver enzymes, lower haemoglobin, albumin and BMI at baseline, elevated plasma efavirenz level, having CYP2B6*6/*6 and ABCB13435TT genotype and slow acetylation status.

ISBN 978-91-7457-629-0