**Proposal for Establishing a Drug-Induced Liver Injury Network at AKUH**

**Background:**

Liver injury as a result of usage of prescribed and non-prescribed medications is a medical, scientific and public health issue of increasing frequency over the past few decades (1). Drug induced liver injury (DILI) is the single most important reason for non-approval, withdrawal, limitation in use and clinical monitoring by Food and Drug Administration (FDA). However, under-reporting of DILI cases, lack of reporting systems, registries and lack of qualified professionals supplemented with difficulty in establishing a clinical diagnosis makes the prevailing system, quite sub-optimal (2). Drug induced liver injury can be severe and even fatal, but it is usually reversed by discontinuation of the offending agent. To continue a medication in the face of drug induced liver injury can have serious consequences (3). Patients who have hepatocellular DILI with jaundice have at least a 10% chance of dying from the injury and DILI patients that progress to acute liver failure have only 25% chance of spontaneous recovery(4). To sum it up, DILI is an uncommon adverse drug reaction of increasing importance to the medical community, pharmaceutical industry, regulatory agencies and the general public.

**Difficulties in Clinical Research in the Field of Drug Induced Liver Injury:**

DILI is a very challenging disease characterized by multiple clinical manifestations and a large spectrum of clinical severity. Data from United States have shown that antibiotics were the drug class mostly frequently associated with non-fulminant drug-induced hepatitis. Diagnosis of DILI requires physicians’ awareness and up to-date knowledge of the condition to generate any sort of suspicion, moreover, the need of clinical skills to critically evaluate the heterogeneous presentation of liver toxicity is also an added challenge. There is a dire need to apply stringent criteria in order to diagnose DILI; indeed, establishing a temporal relationship (causality) between the drugs and liver damage is a difficult task, particularly when the patient is receiving multiple medications including more than one potential hepatotoxic drug.

DILI also lacks specific markers and the intentional drug re-challenge that could confirm a hepatotoxicity suspicion, is unethical and therefore not recommendable. All the above mentioned confounding factors together with the ever-increasing number of reports implicating pharmacological agents and herbs in liver toxicity makes the field of DILI particularly fascinating and difficult. However, the main role of the causality scale evaluation is to assess the temporal relationship between the drug initiation time and development of abnormal liver enzymes and to exclude other causes of liver injury.

Moreover, several circumstances such as pharmaceutical policies and prescription habits, ethnicity, environmental and genetic factors appear to influence not only the incidence, but also the clinical form and DILI’s severity.

**Why is there a Need to Setup a DILI Network?**

Due to the absence of controlled trials and incomplete post-marketing studies, the true incidence of hepatotoxicity is often underestimated. These poorly designed post-marketing studies have generated unreliable data on DILI. The inherited flaws in these analyses have always resulted in the miscalculation of the number of exposed individuals whenever a drug is commercially available.

Nevertheless, for many drugs no post marketing studies have been performed till date. The only way to overcome this lack of information is to first establish a DILI network locally at Aga Khan University Hospital, Karachi and then expand it nationally, regionally and globally.

**How Should the Main DILI Network at AKUH Operate?**

The lack of a central DILI registry where physicians can centralize reports on hepatotoxic events occurring within the city constitutes a major epidemiological deficiency in the liver toxicity field within our country. Information on hepatotoxicity in Pakistan is scanty and usually comes from case reports of the patients. The lack of information regarding the incidence and particular characteristics of DILI makes it necessary to implement a centralized data registry system that would allow us to include data from major tertiary care hospitals within the metropolitan city and record data prospectively over time. Physicians using a structured and uniform protocol, methodologically well-equipped to the protocol, would provide valuable information to identify the characteristics of patients, drugs or herbal medicines more frequently involved in DILI, patterns of liver injury and its associated outcome.

A Drug Induced Liver Injury (DILI) network will be established at Aga Khan University Hospital (AKUH). We will need a desk space either in the Department of Pharmacy or Department of Medicine to fully run the local DILI network. Five major tertiary care hospitals in the city, capturing a large patient population of liver diseases, representing different classes of socio-economic strata will be part of this network. Jinnah Postgraduate Medical Center, Civil Hospital, Karachi, Liaquat National Hospital, Abbasi Shaheed Hospital, Ziauddin Hospital would be the five collaborating hospitals reporting suspected cases of DILI as per define protocol to AKUH.

**Role of Research Assistant Located at DILI Network:**

A research assistant will be hired especially to track and manage data being received from all the five collaborating institutions. At the same time, that person would also be responsible to streamline data being captured from AKUH and maintain a database of all the DILI cases. A hepatologist representing each collaborating institute would be responsible to correspond with the research assistant located at the DILI network in order to ensure smooth data collection from all the five institutions. In case of any discrepancy, Principal Investigator located at AKHU would be informed and a solution would be discussed involving stakeholders from all the affiliated institutions.

Moreover, a centralized web based system will be developed to capture patients with DILI involving funding from Pharma Vigilance pharmaceutical industry. This will ensure proper tracking and reporting of all the DILI patients mainly targeting the five institutions.

**What are the Future Strategies for the DILI Network to perform its Goals?**

1. To establish a registry of DILI cases with annual contact.
2. To refine hepatotoxicity criteria by better weighing clinical information available. Adequate management of these factors will have a significant impact on clinical practice and would have an important bearing in Public Health.
3. Establish new causative mechanisms and to discuss new definitions of DILI phenotypes and outcomes.
4. To perform phenotypic and genotypic studies in order to identify and individualize pathogenic mechanisms specifically related to drug susceptibility, involvingpeople from different ethnic and cultural background (if we have the resources available to meet this objective, might need to involve people from the Department of Biological and Biomedical Sciences).

Figure 1: Schematic Diagram of DILI-N at *Local Level* (Karachi) – **Step 1**

AKU Drug-Induced Liver Injury Network Karachi

Collaborating Hospitals\*:

1. AKUH
2. JPMC
3. CHK
4. LNH
5. ASH
6. ZH

Collaborating Pharmaceuticals:

1. Ferozsons
2. Abbott
3. Sanofi Aventis
4. Getz
5. Highnoon
6. Pharmevo

\* AKUH: Aga Khan University Hospital, JPMC: Jinnah Postgraduate Medical Center, CHK: Civil Hospital, Karachi, LNH: Liaquat National Hospital, ASH: Abbasi Shaheed Hospital, ZH: Ziauddin Hospital

**Step 2:** *National Level* – Extension of DILI-N at local level in collaboration with Pakistan Society of Study of Liver Diseases (PSSLD)

**Step 3:** *Regional Level* – Extension of DILI-N at national level in collaboration with Chinese DILI-N

**Step 4:** *Global Level* – Collaborating this regional network of DILI with National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) main DILI Network

*Eligibility Criteria (5)*

Inclusion Criteria:

1. Adults or children > 2 years old
2. Evidence of liver injury known or suspected to be related to a drug or complementary and alternative medications (CAM) product
3. Written informed consent will be obtained from all the participants to be included in the centralized DILI’s network
4. Documented clinically significant DILI, as shown by any of the following:
   1. Jaundice or serum bilirubin > 2.5 mg/dl and any elevation in ALT, AST, or alkaline phosphatase
   2. No jaundice and serum bilirubin < 2.5 mg/dl, but elevations in ALT or AST (> 5 x Upper Limit Normal) or elevations in alkaline phosphatase (> 2 x Upper Limit Normal)
   3. In persons with known pre-existing liver disease (such as chronic hepatitis B or C), elevations in ALT or AST > 5 x baseline values or elevations in alkaline phosphatase > 2 x baseline values

Exclusion Criteria

1. Paracetamol (acetaminophen) hepatotoxicity
2. Pre-existing liver disease such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis or other chronic biliary tract disease that may confound diagnosis
3. Liver or bone marrow transplant prior to the physician’s visit
4. Identifiable competing cause of liver injury felt to be responsible for observed liver injury

**Dissemination:**

Results from the main DILI network would be compiled on annual basis and shared with the five affiliated institutions. Collaborating institutions would be informed regarding the development of new trends or causative mechanism of the disease through annual report generated from the network. Findings generated as a result would be disseminated through local seminars and workshops. They will also be disseminated through the medium of local and international conferences so that awareness can be created regarding this disease among practicing physicians and the general public.

**Funding Sources:**

Stakeholders of various pharmaceutical industries including; Abbott, Feroz sons, Sanofi Aventis Getz, Highnoon and Pharmevo would be approached for funding with respect to this study. Chief Executive Officer of AKUH would also be approached in order to obtain permission and secure funds with respect to the local setup of DILI network at AKUH. Moreover, a centralized web based system will be developed to capture patients with DILI involving funding from Pharma Vigilance pharmaceutical industry.

**Data Collection Tool (Performa) – Template (6):**

* Patient’s sex and age
* Drug and its dose
* Primary disease (for which drug was prescribed)
* Concomitant diseases (with special mention of heart failure or episodes of hypotension, sepsis, or receipt of parenteral nutrition)
* Pertinent past medical history (including previous exposure to drug, previous reaction to drug or other drugs, history of liver disease, and riskfactors for liver disease)
* History of alcohol use
* Dates of start and discontinuation of therapy (or time from onset of event)
* Symptoms
  1. Date of onset
  2. List of pertinent symptoms (fatigue, weakness, nausea, anorexia, abdominal pain, dark urine, jaundice, pruritus, rash, and fever)
* Pertinent physical findings at the time of presentation (with special mention of whether or not there is fever, rash, jaundice, hepatic tenderness,or signs of chronic liver disease)
* Medication history (other meds taken in the 3 months before onset of liver injury with dose, generic name, and duration)
* Laboratory tests
  1. Date or time of first abnormal laboratory test
  2. Laboratory test results from before drug exposure (specifically liver tests)
  3. Initial laboratory results at presentation (bilirubin, ALT, AP, INR or PT, and eosinophil count or percentage)
  4. Laboratory results needed to exclude other causes (IgM anti-HAV, IgM anti-HBc, HBsAg, anti-HCV, HCV RNA, and ANA)
  5. Course of serum bilirubin, ALT, AP, and INR levels (preferably in a table with entries dated from time of starting and stopping the drug anduntil resolution)
* Imaging studies (abdominal ultrasound, CT, or MR)
* Liver histology results (if obtained and date of procedure in relation to episode of DILI)
* Whether re-challenge with the same medication was done and, if so, results of the challenge.

**Approximate Budget for Establishing and Running a DILI Network**

1. *Space budget:* If a separate desk space for this network is located within the Department of Medicine, then it would be free of cost but if it is located inside the Department of Pharmacy, the spacing cost of one cubical would be approximately Rs. 30,500 per month and it would translate into Rs. 366,000 per annum.
2. *Research Personnel:* A research assistant pay would be around Rs. 30,000 per month and it would amount to Rs. 360,000 per annum.
3. Web-based Reporting: Development of a centralized web-based system of vigilance and reporting of DILI cases. It would nearly amount to Rs. 250,000 (one time cost) and Rs. 50,000 per annum (maintenance cost)

Total Budget Cost (Approximate): Rs. 366,000 (per annum) + Rs. 360,000 (per annum) + Rs. 250,000 + Rs. 50,000 (per annum) = **Rs. 1,026,000**

**References:**

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