Recent global endeavors in the detection and prevention of drug-induced liver injury

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Although drug-induced liver injury (DILI) is not the commonest adverse drug reaction (ADR), it is the single most frequent ADR causing a drug to be withdrawn from the market. It also prompts the preclinical termination of many developing drugs, and limits the use of some drugs after marketing. DILI accounts for more than half of acute liver failure in the USA, and is the leading cause of nonviral acute liver injury in the world. The number of cases of DILI is expected to grow, because of the impacts of progressive new drugs on the market and the burden of global aging.

Most cases of DILI are mild and self-limiting, after discontinuation of the culprit agent. However, severe DILI may be fatal or with permanent sequelae. Early detection and prevention of severe forms of DILI has been a challenge for physicians, pharmacists, pharmaceutical industries, and healthcare administrations globally. This effort commenced 23 years ago when the Russul Uclaf Causality Assessment Method (RUCAM) was designed to be the scoring system for the diagnosis of DILI in the Paris international consensus meeting in 1989. Since then many European countries have begun to survey self-reported DILI cases nationwide. The US Food and Drug Administration (FDA) has hosted an annual DILI conference since 2000. Thereafter, in 2003, the Drug-Induced Liver Injury Network (DILIN) was established in the USA with the support of National Diabetes and Digestive and Kidney Diseases (NIDDK) to collect the data and bio-specimens of patients with severe DILI from 13 medical centers across the mainland.

The first report of 300 enrolled cases from DILIN disclosed that antimicrobial drugs are the leading cause of DILI in the USA (45.5%), followed by central nervous system agents (15%).1 Fourteen percent of patients had developed chronic liver injury, and 8% had died.

Recently, the international Drug-Induced Liver Injury Consortium (iDILIC), set up by the European non-profit international Severe Adverse Events Consortium (iSAEC), has collected bio-specimens and data for DILI globally (mainly from Europe) and published a first multinational genome-wide association study (GWAS) of human leukocyte antigen (HLA) and amoxicillin–clavulanate-induced hepatotoxicity.2 They found some class I and II HLA genotypes may affect the susceptibility and severity of this most prevalent form of DILI in Europe and USA. The other remarkable finding is the GWAS of flucloxacillin-induced hepatotoxicity and HLA from the UK. They revealed patients with HLA-B*5701 have significantly higher risk of having flucloxacillin-induced liver injury (odds ratio = 80.6).3 This highlights the value of genetic studies in understanding the mechanism of DILI and posits a successful model for further clinical application.

In Taiwan, only a few single-center studies about DILI have been reported.4–10 A national database of DILI was not established until 2011 when the Drug-Induced Liver Injury Network in Taiwan (DILINT) was launched, sponsored by the Taiwan Food and Drug Administration (Fig. 1). This is a multi-center collaborative program to collect the clinical data of DILI prospectively and retrospectively from six
media, the preliminary data showed that antituberculosis drugs are the leading discriminated agents (27.8%), followed by herbs (20.5%), and antibiotics (10.0%) (unpublished data). The finding that antituberculosis drugs and herbs play major roles in DILI in Taiwan is consistent with findings in mainland China, Hong Kong, Singapore, Korea and many other countries. This highlights the urgent need for a pharmacovigilance program covering both conventional, Western drugs and herbs.

Global endeavors in the early detection and prevention of DILI have been developed over the past decade, based on the gradually growing database. In addition to the above-mentioned association study of HLA, assaying functional genetic polymorphisms of the target drug-metabolizing enzymes is another way to detect the susceptibility genetic factors of DILI. Since antituberculosis drugs are the leading culprits for DILI in Taiwan and many Asian countries, we have recently performed a series of pharmacogenetic association studies in this field. We found that the Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor of antituberculosis drug-induced hepatitis. Gastroenterol 2008; 135: 1924–34.


