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Editorial – Drug-induced hepatotoxicity

F.P. BUSARDÒ[1], A. GRIECO[2]

[1]Unit of Forensic Toxicology (UoFT) – Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, Sapienza University of Rome, Rome, Italy
[2]Internal Medicine Institute and Internal Medicine and Gastroenterology, Catholic University of the Sacred Heart, Rome, Italy

Drugs represent an important cause of liver injury. Presently, almost 1,000 drugs, toxins, and herbs have been reported to cause liver injury and almost 75% of the idiosyncratic drug reactions result in liver transplantation or death. Various types of drug-induced liver diseases are acute-dose dependent such as liver damage, acute fatty infiltration, cholestatic jaundice, liver granulomas, active chronic hepatitis, liver cirrhosis, liver tumours, etc.[1,2].

Physicians must be vigilant in identifying drug-related liver injury because early detection can decrease the severity of hepatotoxicity if the drug is discontinued. The manifestations of drug-induced hepatotoxicity can be significantly variable, ranging from the asymptomatic elevation of liver enzymes to fulminant hepatic failure. Knowledge of the commonly implicated agents and a high index of suspicion are essential in diagnosis[1-3].

Taking into consideration the importance of drug-induced hepatotoxicity as a major cause of liver damage, this supplement throws light on various drugs which can induce hepatotoxicity, with their mechanism of liver damage and the related clinical scenario. Moreover, special attention has also been given to fatalities following drug-induced hepatotoxicity, by evaluating both the macroscopic findings in the forensic setting and the histological patterns.

Firstly, Marrone et al[4] in their manuscript presented an updated review of diagnostic and classification criteria of drug induced liver injury (DILI). The authors pointed out that despite the advances in the understanding and the characterization of the phenomenon, DILI remains an exclusion diagnosis so that probability scores and the analysis of literature reports represent useful tools in dealing a suspected case. Finally, Marrone et al[4] briefly discussed prognostic tools and principles of DILI management and therapy.

Professor Craxì and his research group[5] reported their clinical experience regarding a prospective cohort of 185 patients with diagnosis of DILI, which were collected from 2000 to 2016. They focused on the frequency of the different drug classes involved in DILI and clinical related outcomes.

Binda et al[6] highlighted in their valuable review the risk of toxicity and drug-to-drug interaction after the introduction of new direct acting antivirals (DAAs), drugs that are effective in combinations without interferon in HCV infection. These drugs are the ones that probably significantly change global landscape of advanced liver diseases in the next few years. The authors conclude that special attention should be given, not only to older patients, but also to those belonging to special populations (e.g. HIV/HCV co-infected subjects and patients with liver and renal impairment). These categories show in fact higher risks of drug-to-drug interaction and toxicity due to the higher number of co-medications and the burden on liver metabolism of the majority antivirals. Therefore, a closer monitoring is recommended in these patients, combined with a strict indication and choice among the different therapeutic regimens.

Corresponding Authors: Francesco Paolo Busardò, MD; e-mail: fra.busardo@libero.it
Antonio Grieco, MD; e-mail: antonio.grieco@unicatt.it

Paracetamol is the most commonly used antipyretic and pain reliever. Paracetamol overdoses are the leading cause of acute poisoning in the United States and represent about 39% of all cases of acute hepatic injury. Furthermore, it is still the almost exclusive cause of liver transplantation related to an acute drug overdose. Tittarelli et al[7] reviewed the most recent studies on paracetamol hepatotoxicity eventually leading to fatalities together with the studies describing other side effects.

Another aspect worthy of attention is the association between drugs and steatosis, described by Miele et al[8]. The authors highlighted that since fatty liver itself is a very common clinical condition, a growing awareness should be paid on the potential risk factor for DILI caused by the underlying metabolic condition.

Malnick et al[9] reported a case involving a 72-year-old female, who developed a submassive hepatic necrosis with the implication of cytokine induction resulting from an immune reaction to denosumab, a fully human antibody to the receptor activator of nuclear factor-KB ligand (RANKL). The authors concluded that for patients with DILI induced by medications, early identification and subsequent withdrawal of the offending agent can improve the prognosis. However, the long half-life of denosumab makes this extremely difficult to achieve.

Giorgetti et al[10] addressed some important ethical and scientific issues related to flutamide-induced hepatotoxicity. The authors underlined that flutamide is responsible for specific hepatotoxic profiles in the female gender. Moreover, from the ethical point of view, off-label prescribing of flutamide in women is not only substantially unlawful, but also, without major safeguards being granted, a potential source of liability for prescribers.

Particularly interesting is the study of Neuman et al[11], who investigated in normal human hepatocytes (NHH) in primary culture possible mechanisms involved in pyrrilidozine alkaloids-induced hepatocytotoxicity in the presence or absence of ethanol (EtOH). Moreover the same authors updated scientific literature on the alkaloids-induced liver toxicity. The results obtained by Neuman et al[11] allowed them to conclude that pyrrilidozine alkaloids up-regulate EtOH-induced hepatocytotoxicity by inducing the inflammatory cytokines and enhancing the apoptotic effects of EtOH.

A paper focusing on hepatotoxicity induced by herbal remedies is the one of Pantano et al[12], who investigated *Chelidonium majus* L. (CM) also known as greater celandine, a plant of the family Papaveraceae, which has been used for a long time in traditional Chinese medicine and phytotherapy as a remedy against several medical complaints.

Biolato et al[13] addressed in their review the difficult issue of inclusion of patients with drug-induced acute liver failure in the list for urgent liver transplant. With this respect, they summarized the different clinical features of drug-induced acute liver failure, the diagnostic work-up, the conservative management and the prognostic scores currently used to list patients for liver transplantation (LT).

Ponziani et al[14] focused on etiology, clinical presentation and therapy of post-liver transplant intrahepatic cholestasis. The authors showed how intrahepatic cholestasis in LT recipients is a challenge for clinicians, as multiple conditions may alter the clinical picture. In this scenario, DILI remains the most common cause of post-LT cholestasis, especially in the late period. The same authors recommended a thorough investigation of medical history in order to exclude a possible DILI. If on the one hand the identification of a drug responsible for cholestasis may be very difficult in the early postoperative period, on the other it can be easier in the late post-LT period, when pharmacological therapy is almost stable. However, the major part of medications is proved as necessary and treatment modifications should be made considering potential drug-to-drug interactions under close clinical monitoring.

Finally, two reviews by Graziano et al[15] and Solimini et al[16] focused on sildenafil and anabolic androgenic steroids, which find broad clinical applications but are often also abused in different contests. In both manuscripts, studies reporting liver toxicity in humans and in animals and the relative risk associated to these substances were described and broadly discussed.

To conclude this special issue, Solimini et al[17] reviewed the recent literature on the synthetic cannabinoids (SCs) toxicity with particular attention to liver damage aspects. Although only a few cases of SCs use have also been associated with liver failure, this has been a first attempt to describe the risk on the most used New Psychoactive Substances which may pose a "public health threat"[17,18], in most cases completely unknown.

We hope that this special issue represents a valuable contribution to the clarification, circulation and advancement of knowledge currently available on different drugs and classes of substances which can induce hepatotoxicity, with their mechanism of liver damage and the related clinical scenario.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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