

Drug Induced Liver Injury (Dili) and Non Alcoholic Fatty Liver Disease (Nafld)

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Abstract — This review article includes a review of the latest literature searched on PubMed in the field of hepatotoxicity caused by drugs that have a wide daily application. The concept of the review article consists of several parts dealing with the definition of drugs induced liver injury - DILI, diagnostic challenges related to it, and the clinical spectrum of liver disease, with an emphasis on the development of nonalcoholic fatty liver disease - NAFLD and review of drugs involved in formation of NAFLD.

Index Terms — DILI, NAFLD, RUCAM, hepatotoxicity.

I. INTRODUCTION

The term “drug-induced liver injury” (DILI) is a broad concept that also includes food-induced liver damage as well as dietary supplements and other nutrients [1]. The overall concept, including manifestation, early recognition, diagnosis and treatment of this is not well understood yet. In essence, it can be said it is based on the principle of exclusion. When all potential known etiologic agents as possible causes of liver damage are excluded, then a diagnosis of DILI can be made [2]. This is certainly a major challenge for every healthcare system worldwide, as it requires extensive diagnostic treatment of patients, which is correlated with the increase in financial allocations for the same purposes, and great expertise in clinicians who have already encountered similar cases, i.e. experience with DILI [3]. DILI is present in every country around the world, with different incidence and prevalence, which have not been precisely defined yet. As to why, is it still difficult to give a definite answer. It is assumed that some health systems are more developed and richer than others, have more clinical experience with DILI, and the number of people using the resources of one health system varies from country to country. Different treatments play an important role too, given that still some healthcare systems adhere to traditional treatment modalities [4], [5].

When analyzing the data of published studies in the last three decades, it can be concluded that the highest incidence is in Asian countries (about 90 per 100,000), while in European countries the incidence ranges from 2.4 in the UK, Italy 4.1, 13.9 in France to 19.4 in 100,000 in Iceland [6],

[7]. The highest incidence in Asian countries is probably due to traditional medicine and the use of herbs and herbal supplements for therapeutic purposes. This type of treatment is not common in European countries but owing to the wide range of non-evidence-based medicines available in many online stores, this incidence is expected to increase in Europe as well [8], [9].

II. CHALLENGES IN DIAGNOSING OF DILI

A peculiar challenge in identifying and diagnosing DILI is the treatment of a known liver condition and the consequential therapy. Patients with a known liver disease may have abnormalities in the hepatogram, like an increase in liver enzymes, for two reasons: the first one is due to the undesirable effect of the drug; the second can be ascribed to the latency phase of a silent hepatic disease, without any clinical presentations [10]-[12].

The link between medication and an already-known liver disease is not well known, and great efforts are still being made to investigate it. So far, two types of drug-induced liver damage have been known and described, the idiosyncratic and intrinsic type [2]. The idiosyncratic type of damage is consequential to taking the drug at the usual therapeutic dose and an unexpected reaction occurs, which may be metabolic or immunological. This type of reaction is usually manifested by the type of delayed reaction. Some studies have proven that a delayed type of reaction by type of idiosyncrasy could occur after taking amoxicillin with clavulanic acid for therapeutic purposes. Such a reaction could occur after a few weeks, or another cases, like with the use of nitrofurantoin, after a few months. At the tissue level, this type of reaction can be evinced by the onset of inflammation, and clinical abnormalities in hepatospecific enzymes, their increase, fever, urticaria, indigestion or eosinophilia in differential blood counts [4], [6], [13]-[15]. Intrinsic type is a type of predictable reaction to a drug that is usually taken at a dose higher than the usual dose. An example of this type of reaction is the abnormal response to paracetamol in some patients [2].

At the tissue level, manifestations include necrosis or programmed cell death-apoptosis, while signs of inflammation are almost absent [13], [14]. Whether either of the two above-mentioned kinds of inflammation is present, both can lead to acute liver failure that requires immediate transplantation [16].

Diagnosis of DILI is a major challenge and, as mentioned above, it is based on the principle of exclusion. After taking a history of the present or previous diseases, as well as current therapy, after having obtained results of laboratory parameters, the current issues can then be analyzed. Laboratory parameters in DILI include the increase of the

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levels of liver enzymes, which can be higher by multiple times and it is also correlated with drug intake, early liver damage, possible drug interactions in polypharmacy and or drink/drug interactions, most commonly alcohol. Based on the increase in the value of the hepatospecific enzymes AST and ALT, the cholestatic enzymes GGT and ALP, and bilirubin, it can be concluded whether this is a hepatocellular, cholestatic or mixed type of damage [13], [14], [17]. If the ratio (R) between ALT and ALP is more than five times, then a hepatocellular type of damage can be taken into account; if it is less than two times, a cholestatic damage can be regarded [18]. There are numerous updates to the guidelines, the most recent of which indicates that DILI can be suspected when ALT is five times higher than its normal values and ALP is two times higher; moreover, it can be contemplated the increase in ALT three times higher its normal level, combined with the increase in bilirubin in more than double its normal value [19], [20]. After having examined laboratory diagnostics and differentiated the type of tissue damage in the liver, the exclusion of large and small hepatotropic viruses, HAV, HBV, HCV, CMV, EBV, as well as HSV, VZV should be performed through the determination of autoantibody titles such as AMA, ANA, pANCA, cANCA, ASMA, LKM, and immunoglobulin values [21]-[26]. Significant helps in diagnostics, such as ultrasound, fibro scan, computed tomography (CT), nuclear magnetic resonance imaging (NMR), liver biopsy and pathohistological verification of the disease must be considered [26], [27].

Thanks to RUCAM (Roussel Uclaf Causality Assessment Method), it is partly easier to reach a diagnosis of DILI. Data quantitatively evaluated at RUCAM are: latency period length, recurrent increase in hepatospecific enzymes, risk factors, individual co-medication, alternative causes, markers of large and small hepatotropic viruses, evaluation of cardiac hepatology, imaging diagnostics of liver and biliary tree, hepatic doppler diagnostics, data on previous hepatotoxicity and toxic substance exposure. The cumulative value of the score obtained is stratified in the range of -3 to +14; according to the value obtained, the probability that a drug has led to DILI is classified as highly probable, probable, possible, less probable or excluded [23], [28], [29].

III. THE CONCEPT OF NAFLD AND DIAGNOSING OF DILI IN NAFLD PATIENTS

The NAFLD (non-alcoholic fatty liver disease) phenotype can entail two different entities, namely NAFL (non-alcoholic fatty liver) and NASH (non-alcoholic steatohepatitis). While NAFL implies the presence of non-inflammatory steatosis, NASH is defined as the presence of inflammatory steatosis and hepatocyte damage [30].

NAFLD is a manifestation of metabolic syndrome and is commonly associated with obesity, dyslipidemia and type 2 diabetes. NAFLD is the most common cause of chronic liver damage in the USA, affecting 1/3 of the population [31], [32].

Hepatic steatosis (NAFL) is defined as the deposition of fat within hepatocytes. There are two types of steatosis: the microvesicular one is characterized by the accumulation of multiple individual fat droplets within the hepatocytes and

centralization of the nucleus, while macrovesicular steatosis is characterized by the appearance of a large fat vesicle that pushes the nucleus towards the periphery of the hepatocyte. The diagnosis of DILI in patients with NAFL/NASH is made on the basis of the following criteria: biochemical and histological indicators of hepatic impairment, time frame from exposure to the onset of the first signs of hepatic impairment, data on improvement of hepatic function after discontinuation of therapy [33].

Among all the scoring systems, RUCAM is the most accurate in diagnosing of DILI in NAFLD patients [34], [35].

IV. THE CLINICAL SPECTRUM OF LIVER DISEASE AND HOW NAFLD IS FORMED

The clinical spectrum of liver disease comprises several clinical entities: steatosis, steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Steatosis, or non-alcoholic fatty liver, is the most common liver disease with a prevalence of between 20 and 30% and has been increasing over the last decade. In some cases, the prevalence ranges from over 50% in obese or diabetic patients. In rare cases, drugs are the cause of DILI; some authors suggest that in less than 2% of cases [36]-[38]. The accumulation of fat droplets within hepatocytes is a foreign body to the immune system at the cellular level, thus inducing the chemotaxis of leukocytes and other cells and leading to an inflammatory reaction with consequential interleukin and mediator formation, then causing steatohepatitis. Steatosis and steatohepatitis in a particular segment are conditions that can be halted before complete liver damage occurs [39], [40]. Long-chain free fatty acids (FFAs) enter the respiratory chain of the mitochondria due to the transport mechanism, reacting with coenzyme A, and the process of β -oxidation leads to the formation of acetyl-CoA. If β -oxidation inhibition occurs, the FFA concentration will increase, which inevitably leads to the synthesis of triglycerides (TGs) by the esterification process. Transport of triglycerides as VLDL may be blocked by some drugs, resulting in the formation of ROS. Certain drugs damage mtDNA. The progression of steatosis to steatohepatitis occurs due to disorders in the level of β -oxidation of fatty acids and increased production of ROS with consequent formation of mediators. Failure to stop exposure to the toxic knockout process inevitably leads to fibrosis and later cirrhosis [41]-[45]. A pharmaco-epidemiological prospective study group of Indiana authors suggests that individuals with CLD such as NAFLD are at increased risk for developing DILI in the United States, up to four times higher risk for patients with NAFLD for DILI than patients with hepatitis C [46].

In an Italian prospective study by Tarantino G et al., 74 patients had NAFLD. Six patients in this group had acute hepatitis associated with the following drug groups: antihypertensive, antiplatelets, antimicrobial, PPI, and NSAIDs. This group of authors also suggest that NAFLD is characterized by mitochondrial dysfunction, which has the same basis as DILI occurring in middle-aged usually obese people [47].

V. DRUGS INVOLVED IN FORMATION OF NAFLD

The drugs that cause NAFLD are divided according to the type of steatosis they cause, microvesicular or macrovesicular steatosis. The action of the drug may affect one of the biosynthetic processes, such as increased mitochondrial permeability, inhibition of fatty acid oxidation, oxidative phosphorylation, direct inhibition of the mitochondrial respiratory chain and depletion, or mtDNA damage. The precursors of drugs that lead to microvesicular

steatosis are paracetamol/acetaminophen, NSAIDs (ibuprofen, naproxen, diclofenac, and aspirin), zidovudine/stavudine, and tetracyclines. Macrovascular steatosis is caused by methotrexate, tamoxifen, 5-fluorouracil, and glucocorticoids. Amiodarone and valproate can cause both types of steatosis. The Table 1 presents the drugs that most commonly lead to NAFLD and the mechanism of their action [48]-[63].

TABLE 1: Drugs Causing Steatosis And Steatohepatitis

DRUG	Type of steatosis	MPTP opening	Direct inhibition of mitochondria FAO	OXPHOS uncoupling	Direct inhibition of the MRC	mtDNA depletion/damage
Acetaminophen (APAP)	microvesicular	+			+	+
NSAID (Ibuprofen and naproxen)	microvesicular				+	+
NSAID (diclofenac)	microvesicular	+	+		+	
NSAID (aspirin)	microvesicular	+	+		+	
Valproat	microvesicular and macrovesicular	+	+			
Zidovudine/Stavudine	microvesicular					+
Tetracycline	microvesicular		+			
Amiodaron	macrovesicular and microvesicular	+	+		+	+
Methotrexate	macrovesicular		+		+	
Tamoxifen	macrovesicular		+		+	+
5-fluorouracil	macrovesicular		+			
Glucocorticoids	macrovesicular		+		+	

Abbreviations: MPTP: mitochondrial permeability transition pores; FAO: fatty acid oxidation; OXPHOS: oxidative phosphorylation; MRC: mitochondrial respiratory chain, mtDNA: mitochondrial DNA.

Amiodarone is an antiarrhythmic drug considered to be a hepatic mitochondrial toxin that inhibits both enzyme complexes into electron transport by acting on β -oxidation. It is clinically presented with an increase in serum transaminases in 40-80% of cases. Histologically, it is characterized by steatohepatitis, balloon degeneration, and inflammatory PMN inflation, as well as micro vesicular seatosis [64], [65].

Aspirin leads to microvesicular steatosis by blocking the process of β -oxidation of fatty acids and increasing mitochondrial permeability. Aspirin used in young children for viral infection therapy can lead to Reye syndrome, manifested by β -oxidation of fatty acids and increased ureagenesis, ketogenesis, and severe hypoglycemia due to the inability to convert lactate into glucose. Diffuse microvesicular steatosis was seen in advanced fatal disease [66], [67].

Tetracyclines were administered intravenously until 1991 when they were found to lead to fulminant hepatitis, which often proved to be fatal. The principle of action was based on inhibition of VLDL secretion and inhibition of β -oxidation [68].

NSAIDs are the leading causes of hepatotoxicity and can lead to hepatocellular or holeostatic type of damage that ends in acute liver failure. Only some have been shown to cause steatosis, most commonly proxene and ibuprofen [69], [70]. Methotrexate is a folate antagonist. It is used as a chemotherapeutic and immunosuppressant in the treatment of IBD, psoriasis and RA. Its hepatotoxic effect is

cumulative and its range of toxicity ranges from steatosis/steathepatitis, focal necrosis to even cirrhosis. Methotrexate also inhibits mitochondrial electron transport [71]-[73].

Glucocorticosteroids are immunosuppressive used in the treatment of autoimmune diseases. Long-term administration causes weight gain, dyslipidemia and glucose intolerance with worsening metabolic syndrome leading to steatosis and steatohepatitis. They inhibit β -oxidation of fatty acids, reduce triglyceride secretion and induce fat peroxidation [74].

VI. CONCLUSION

The findings to date, and the retrospective and prospective studies conducted, raise the suspicion of an increase in the incidence of DILI in patients with NAFLD, especially middle-aged people with metabolic syndrome. There are uncertainties regarding the setting of precise DILI diagnostic criteria due to the inability to understand the causality of the current presentation of hepatic lesions. Because of this reason, DILI remains a diagnosis that is deducted by the principle of exclusion.

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