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Drug induced liver toxicity–where we are?

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Abstract

Drugs are the one of the major cause of liver injury. Because with some exception all drugs are metabolized by the liver it carries inherent risk of injury or toxicity. Various Xenobiotics by various ways affect the liver, many drugs produces acute liver injury that liver may repair itself because of its fast regenerating property. DILI classified as acute, Idiosyncratic and chronic on the basis of there mechanism and duration of toxicity. Some common agents that can cause liver injury are acetaminophen, antibiotics, statins, INH and herbal drugs with different modes and duration to affect the liver. Many drugs not affect the liver when taken for short duration but on continuous consumption they leads to disruption of hepatocytes. The obvious fact that different drug utilises different enzymes to get metabolised the toxicity produced by them also varies. The liver toxicity from drugs ranges from mild injury to total dysfunction of liver. In this review we have discussed the various pathologies underlies the liver injury induced by the drugs including polymorphism, autoimmune and hapten hypothesis with the summary of drugs which are proven hepatotoxic till date.

Keywords: Liver injury • Xenobiotics • Xenobiotics • Hepatocytes

Introduction

There are many and thee will be many more drugs proven to be toxic to the liver. There are more than 1000 drugs which are hepatoxic. As we know that liver is the main organ for metabolism of the xenobiotic. There are many enzymes in liver which are responsible for the metabolism of the xenobiotic into its metabolites ex. CYP1A2, CYP2A6, CYP2B6,CYP2C8,CYP2C9,CYP2C19,CYP2D6,CYPE1,CYP2J2,CYP3A4/5. But sometimes metabolites produced are hepatotoxic. There are many enzymes which shows genetic polymorphism is another major factor for liver injury [1].

Materials and Methods

Classification of Drug induced liver injury

Intrinsic DILI (TYPE1): As name indicate its intrinsic when the drug dose goes beyond the limit or threshold dose, where all the metabolising enzymes get saturated leads to liver injury. As its dose dependent consequences of it are predictable and becomes severe when the dose increased. Ex. Acetaminophen, Anabolic steroid, anti-metabolites, cholestyramine, cyclosporin, valproic acid, HAART drugs, nicotinic acid, tacrine, Statins,

Idiosyncratic DILI (TYPE2): It's because of the genetic susceptibility of the subject and it man or may not be dose dependent. The consequences of such injury are unpredictable because is the genetic polymorphisms so the severity varies amongst the susceptible individual and exibit variable latency to onset (Days to Weeks) .

Ex. Allopurinol, Diclofenac, Disulfiram, Isoniazid, Ketoconazole, Leflunomide, Lisinopril, Methyldopa, Phenytoin, Tolcapone, Nitrofurantoin.

Both Intrinsic and Idiosyncratic DILI causing agents: Amiodaron and Statins

Chronic DILI: When drugs taken for long duration result into cumulation and leads to DILI. Irreversible depletion of liver enzymes leads to liver disease. Chronic DILI starts from the acute liver failure acute jaundice cirrhosis finally death (Figure 1).

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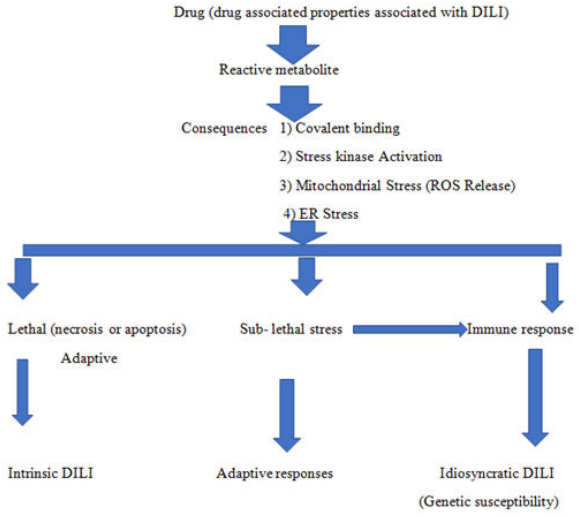

Figure1: Mechanism based interrelation between intrinsic and idiosyncratic DILI.

Class of drugs	Examples
IMMUNOMODULATORY DRUGS	Azathioprine/6-mercaptopurine, infliximab, interferon beta, methotrexate and thioguanine. Antineoplastic: Busulfan, floxuridine and flutamide
ENDOCRINE SYSTEM AFFECTING DRUGS	Anabolic androgenic steroids, estrogens/ progestins and propylthiouracil.
CENTRAL NERVOUS SYSTEM	Carbamazepine, Chlorpromazine, Dantrolene, halothane, phenytoin and valproate.
RHEUMATOLOGIC DRUGS	Allopurinol, auronofin/Gold products, diclofenac, ibuprofen, nimesulide and sulindac
ANTIMICROBIALS DRUGS	Amoxicillin-clavulanate, erythromycin, flucloxacillin, interferon alpha/ peginterferon, isoniazid, ketoconazole, minocycline, nevirapine, nitrofurantoin, pyrazinamide, rifampicin, co-trimoxazole, and sulfonamides.
CARDIOVASCULAR DRUGS	Carbamazepine, Chlorpromazine, Dantrolene, halothane, phenytoin and valproate.
MISCELLANEOUS	Disulfiram and ticlopidine

Table1: Examples of idiosyncratic dili.

Risk factors related dili in humans: For the development of DILI not only drug is responsible although drug is primary causal factor after that DILI is sustained and influenced by the host factor as well [2].

Drugs related risk factor

Dose and hepatic drug metabolism: Intrinsic DILI is dose dependent so dose is determining factor in this case. Idiosyncratic DILI is were considered to be non-dose dependent but the basis of drug dose plays a role in idiosyncratic DILI was first demonstrated in a study of 598 Swedish DILI cases reported to the Swedish Adverse Drug Reaction Advisory Committee, which found that 77% of the cases involved a causative agent given at a dose ≥50 mg/day while 10mg/day was not associated with DILI. Drug dose increased beyond threshold leads to increased amount of toxic metabolites and metabolic enzymes may get saturate leads to accumulation of drug in liver leads to DILI.

Lipophilicity: Higher the lipophilicity higher the potency but sometimes it also leads to off-target binding which further strengthen the events of DILI. Lipophilicity plus drug dose considered as "RULE OF TWO" suggested to reflect a drug's hepatotoxic potential, with high lipophilicity (LogP >3) and daily dose (>100 mg) being associated with increased risk of DILI, based on an analysis of 164 approved medications in the US [3].

Concomitant drugs, potential interactions: one should keep in mind this that simultaneous administered medications are not always beneficial but can also affect DILI susceptibility through drug-drug interactions. Concomitant drugs are capable of modulating the metabolism of other drugs through induction, inhibition or substrate competition, in particular of CYP reactions.

Ex. Rifampicin+ Isoniazid = Increased hepatotoxicity

Anticonvulsant (Carbamazepine, Phenytoin) + Valproic acid=Increased liver toxicity. The reason behind this is assumed to be the increased production of 4-ene valproic acid and (E)-2,4- diene valproic acid, caused by the concomitant anticonvulsant drugs that might be related with enzyme induction [4].

Reactive metabolites and oxidative stress: Reactive metabolite formed by the enzymatic action on drug have significantly hazardous impact on cell organelles. In addition to their direct toxic effect, reactive metabolites are considered a first step in the onset of idiosyncratic DILI since the covalently bound proteins form immunogenic haptens (Incomplete antigen)which can trigger a downstream immune response.

- Diclofenac forms Reactive quinone imines by CYP2C8, CYP3A4 and activation to acyl glucuronides by UDP-glucuronyl transferase (UGT) 2B7.
- Ibuprofen forms Acyl glucuronide metabolite
- Acetaminophen forms the hepatotoxic metabolite of acetaminophen, NAPQI (N acetyl para benzquinone imine), oxidizes proteins thiol groups and generates ROS.
- Lumiracoxib causes hepatotoxicity structurally resembles diclofenac and also forms reactive quinone imines.
- Troglitazone, which forms a reactive quinone metabolite
- Other drugs forms reactive metabolites include
- Clozapine
- Tolcapone
- Nefazodone,
- Zafirlukast,
- Tamoxifen,
- Flutamide,
- Amodiaquine,
- Sulfamethoxazole,
- Isoniazid,
- Terbinafine,
- Felbamate,
- Halothane
- Carbamazepine

Mitochondrial Hazard: Microvesicular steatosis is seen with amiodarone, valproate, tetracycline and various antiviral nucleoside analogues and is characterised by reduced numbers of mitochondria. valproic acid inhibits the mitochondrial beta oxidation.

Hepatobiliary transport inhibition : Bile acid export pump(BSEP) Inhibition leads to drug-induced cholestasis and has been reported for cyclosporine A, rifampicin, bosentan, troglitazone and various other compounds [5].

Host dependent risk factor

Age: As the age increases there is changes in various parameter related with pharmacokinetic and pharmacodynamic so chances of hepatotoxicity is more in elder people. Impaired clearance, hepatic metabolism, change in body composition.

Gender: A prospective, multicentric study based on pharmacovigilance involving 2,371 patients for whom 25,532 drugs had been prescribed has confirmed a higher possible risk of ADR among female subjects than a male cohort. This may be because gender-dependent differences in pharmacokinetics and pharmacodynamic after the administration of certain drugs, gender-based hormonal effects or interaction with signaling molecules that can affect drug safety, and differences in an aberrant immune response that targets the liver following drug exposure that can result in adverse drug reactions. Studies in murine liver models have identified more than 1,000 genes whose expression is dependent, and their gene products include many drug metabolizing enzymes (DMEs). This clearly reflects the why women are more susceptible to DILI.

Race: The Epigenetic term has evolved to include any process that alters gene activity without affecting or altering the DNA sequence, and leads to modification in the response to the drug metabolism. Many types of epigenetic processes have been identified—they include methylation, acetylation, phosphorylation. It has been shown that association of gene polymorphism associated with specific drug induced or group of drug induced liver toxicity. **Ex.** HLA gene associated DILI.

Genetic variation or differences associated with race

Amoxicillin and Clavulanate-Associated DILI-Two novel genetic factors associated with amoxicillin/clavulunate induced DILI: HLA-A*02:01 [odds ratio 2.2 (95% CI 1.6– 3.2)] in all patients and HLA-B*18:01 which is same like carbamazepine induced severe skin irritation(in Asian people) associated with HLA-B*15:02.

Flucloxacillin-Associated DILI- Related with strong association with HLA-B*57:01

Minocycline-Associated DILI - This study reported a significant association between HLA-B*(35:02).

Alcohol and Pregnancy: Alcohol is a CYP2E1 inducer and plays crucial role in the formation of N-acetyl-p-benzoquinone imine (NAPQI), the reactive metabolite responsible for acetaminophen hepatotoxicity. Data in support alcohol associated idiosyncratic DILI are only available for few drugs, such as isoniazid, methotrexate and halothane. In pregnancy there is higher incidences of DILI because of the changes in the hormonal level and other physiological parameter. High frequency drugs administration in women prior-during-after the pregnancy again predisposes them to DILI. For abnormal LFT (Liver function test) in pregnant women drug-induced liver injury (DILI) from prescribed and over-the-counter medications, herbal supplements and remedies, and even mushroom poisoning have been reported [3].

Underlying Diseases: Presence of chronic liver disease, Non-alcoholic liver disease patients are at high risk for developing DILI. Hepatitis and jaundice also favour's the DILI.

Genetic Polymorphism: Its of special concern in the context of Antitubercular drugs. Isoniazid causes liver injury in patients with polymorphism in NAT2(N Acetyl transferase) and CYP2E1.Fast acetylators are at lower risk to Antitubercular liver injury compared to slow acetylators. Additionally glutathione related null GSTM1 or GSTT1 genotypes could not detoxify the toxic reactive metabolites efficiently, and thus have higher risk of drug-induced liver injury as seen with Tacrine and troglitazone.

Genetic polymorphism in the following enzymes leads to DILI

CYP450: Acetaminophen (CYP2E1, CYP1A2 and CYP3A), Perhexiline (CYP2D6), Ticlopidine (CYP2B6), efavirenz (CYP2B6*6).

UDP-glucuronosyltransferases (UGT): Idiosyncratic reaction induced by Diclofenac (UGT2B7) and Tolcapone (UGT1A6).

N-acetyltransferase 2: Well known example this is isoniazid, Acetylhydrazine, an isoniazid metabolite which can undergo metabolic conversion through cytochrome P450 to a toxic metabolite or by NAT2 to the less toxic diacetylhydrazine, so the slow acetylators or absence of NAT2 activity people are at higher risk for isoniazid toxicity.

ABC Transporters: BSEP encoded by ABCB11, MPR2 Encoded by ABCC2(important for bile acid transport), MDR1 coded by ABCB1, other ABC transporters, MRP3 and MRP4 encoded by the ABCC3 and ABCC4 genes. Any polymorphism in these transporters leads to various liver injuries accompanied by the drugs. Sometimes drugs inhibits the transporters and leads to accumulation bile acid as in case of Troglitazone and sulfate metabolite inhibit both BSEP and MRP4 leads to cholestatic DILI [5].

There are so many drug which are failed to obtained marketing approval because of liver injury accompanied by their use but more importantly there are drugs which are banned after marketed for some time period following are some examples of those.

From 1997 to 2016, eight drugs were withdrawn from the market because of hepatotoxicity reason tolcapone troglitazone, trovafloxacin, bromfenac, nefazodone, ximelagatran, lumiracoxib and sitaxentan.

Results

Micro-level mechanism of DILI

Drug induced liver injury mechanism can be divided into two pathway but the exact mechanism of each drug causing hepatotoxicity remain unclear.

Direct Hepatotoxicity: Direct hepatotoxicity is caused by the direct action of a drug, or its reactive metabolite, against hepatocytes. One hugely studied drug used to examine the mechanisms of hepatotoxicity is APAP. APAP is a popular OTC analgesic that is safe at therapeutic doses but at overdose can leads to centrilobular hepatic necrosis, which may lead to acute liver failure and if used for prolonged period with high doses leads to chronic liver failuare. APAP is metabolized to a minor electrophilic metabolite, N-acetylp-benzoquinoneimine (NAPQI), during APAP overdose depletes glutathione (because of formation of high quatity of toxic NAPQI) so this metabolite can't be neutralized by it and this displaced metabolite covalently binds to cellular proteins. These events lead to the disruption of calcium homeostasis, mitochondrial dysfunction, and oxidative stress and may eventually result in cellular damage and death. Fortunately, drug candidates having hepatotoxic potential at therapeutic doses usually detected in preclinnical and clinical trial so they are eliminated from released into market In most instances of DILI, it appears that hepatocyte damage leads to the activation of other cells, which can initiate an inflammatory reaction and/or an adaptive immune response. These secondary events may attenuates the capacity of the liver for adaptive repair and regeneration, thereby contributing to the pathogenesis of liver injury. So this means direct hepatotoxicity takes help of adverse immune reaction mechanism to cause severe liver damage. Hepatocyte death is the main step to liver injury, although sinusoidal endothelial cells or bile duct epithelial cells may also be targets. They may also indirectly influence cellular organelles through the activation and inhibition of signaling kinases, transcription factors, and gene-expression profiles.

It is possible that toxic metabolites undergoing canalicular excretion react with macromolecules in the ductcells or undergo further metabolism within these cells, resulting in ductal inj

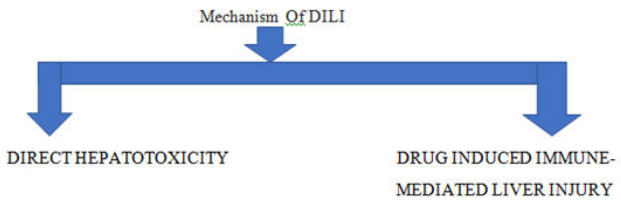

Figure2: If a drug metabolite from cytochrome P450 is able to act as a hapten, it would covalently bind to a liver protein and, alter that protein to make it complete antigen.

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Drug-induced immune-mediated liver injury

Livers continuous exposure to pathogens, toxins, tumor cells, and harmless dietary antigens, it possesses a range of adaptive and innate immune mechanisms to cope with these challenges. In addition to that regional population of macrophages (KC), NK cells, and NKT cells also there to fight against foreign matter. The liver also possesses a unique combination of intrahepatic lymphocytes, which include not only the conventional CD4 + and CD8 + T cells but also high percentages of gamma delta T cells and CD4 – CD8 – T cells. So the innate and adaptive immune cells contribute to the unique immune responses of the liver, including removal and destruction of pathogenic microorganisms, clearance of particles and soluble molecules from circulation, deletion of activated T cells, and induction of tolerance to food antigens derived from the gastrointestinal tract. KC play an essential role in the phagocytosis and removal of pathogens entering the liver *via* portal-venous blood. Upon activation, KC produce various cytokines and other mediators, including prostanoids, nitric oxide, and reactive oxygen intermediates. but its obvious that when KC produces tehse mediators against the drug then it will result into to strenthening of liver injury. These KC products play major roles in promoting and regulating hepatic inflammation. when regulation is hampered leads to promotion of drug induced liver injury. KC cell also regulates the amount of NK and NKT cells.

Role of innate immunity in DILI

Drug-induced stress damage of hepatocytes may trigger activation of inflammatory and also proinflamatory responses of the innate immune system within the liver. studies of liver injury induced by overdose of APAP, which is one of the few drugs that provide an experimental animal model of DILI. There is growing evidence that the initial NAPQI-induced hepatocyte damage may lead to activation of innate immune cells within the liver,stimulating hepatic infiltration of inflammatory cells. Activated cells of the innate immune system produce a range of inflammatory mediators, including cytokines,

chemokines, and reactive oxygen and nitrogen species that contribute to the progression of liver injury. Some of these mediators, such as IFN- , Fas, or Fas ligand (DILI Facilitating role), are directly involved in causing liver damage through apoptosis in mutant mice lacking these factors are resistant to APAP hepatotoxicity.On the other side, the innate immune cells also represent a major source of hepatoprotective factors, as it has been demonstrated that transgenic mice deficient in IL-10, IL-6, or COX-2(Protective role) are more susceptible to APAP-induced liver injury.

Role of adaptive immune response in DILI

The distinct clinical features of some cases of DILI strongly suggest an involvement of the adaptive immune system. Like concurrence of rash, fever, and eosinophilia, delay of the initial reaction (1-8 weeks) or requirement of repeated exposure to the hepatotoxic drug, rapid recurrence of toxicity on reexposure to the drug, presence of antibodies specific for native or metabolite. Drugs acts through this reactions include halothane, tienilic acid, dihydralazine, diclofenac, phenytoin, and carbamazepine.

Hapten hypothesis of DILI

Drug–protein adducts, which an immune response. These peptides are presented on the cell surface of macrophages in complex with major histocompatibility complex (MHC) class II molecules. The adaptive immune response (consisting of CD4+ and CD8+ T cells) to such adducts contributes to the apoptosis of hepatic cells mediated through Fas ligand (Extrinsic mechanism of apoptosis). For example, both halothane and tienilic acid can lead to the formation of circulating antibodies to liver and kidney endoplasmic reticulum (anti-liver and/or kidney microsomal [anti-LKM] antibodies). These antibodies are formed as a result of an acquired immune response to a new antigen created by the covalent binding of a reactive metabolite and a hepatocellular protein (Haptenization). Anti-LKM antibodies frequently react with CYP isoenzymes and might also react with other drug metabolizing enzymes. The presence of biomolecule at particullar extent because of existing infection leads to the induction of liver injury to otherwise safe drugs.Thats the reason behind the patients with AIDS more susceptible to drug related ADRs. Beyond this immune mediated reaction transcriptional events that might provide insight into the pathogenesis of DILI, as shown for acetaminophen. Understanding the molecular and cellular elements in immune mediated or haptenization mediated DILI models can help identify risk factors, and ultimately facilitate the development of prediction and prevention strategies.Although reactive metabolite leads to DILI but Not all reactive metabolites are associated with the same risk of causing Idiosyncratic DILI. If the reactive metabolite has potential to cause some cell damage, this can lead to the release of danger-associated molecular pattern molecules (DAMPs) that activate APCs. However, the hapten hypothesis encounters difficulties in explaining how drug-protein adducts result in immune reactions that cause liver injury. Many drugs form reactive metabolites to some degree; however, they have rarely been associated with overt immune toxicity, as exemplified by acetaminophen, thioacetamide, isoflurane, and desflurane. Even for the drugs that cause immune-mediated DILI, the hapten hypothesis does not explain the mechanism. One major reason preclinical models fail to detect intrinsic DILI liability is each drug has its different metabolism and disposition pathway (Tables 2-3).

Signature disease	Drugs causing the feature
Acute Hepatitis	Acetaminophen, Nevirapine, Ritonavir, Troglitazone, Isoniazide
Chronic Hepatitis	Dantrolene, Diclofenac, Methyldopa, Miocycline, Nitrofurantoin
Acute Cholestasis	ACE inhibitor, Amoxicillin/clavulanic acid, Chlorpromazine, Erythromycin
Mixed or Atypical Hepatitis	Phenytoin, Sulfonamide
Nonalcoholic Steatohepatitis	Amiodarone, Tamoxifen
Fibrosis/cirrhosis	Methotrexate
Microvesicular Steatosis	NRTIs, Valproic Acid

Table2: Diseases like feature from DILI.

Type of Injury	Causative drug
Granulomas Neoplasms adenoma Anabolic steroids; oral contraceptives angiosarcoma Anabolic steroids cholangiocarcinoma Anabolic steroids hepatocellular Danazol carcinoma Non-alcoholic Amiodarone; tamoxifen steatohepatitis Phospholipidosis Amiodarone Vascular lesions Budd-Chiari syndrome Oral contraceptives peliosis hepatis Anabolic steroids; azathioprine; oral contraceptives perisinusoidal fibrosis Retinol (vitamin A) veno-occlusive disease Busulfan; cyclophosphamide	Allopurinol; amoxicillin/clavulanic acid; carbamazepine; hydralazine; methyldopa; penicillamine; phenylbutazone; phenytoin; procainamide; quinidine; sulfonamides
Neoplasms - adenoma - angiosarcoma - cholangiocarcinoma - hepatocellular Carcinoma	Anabolic steroids; oral contraceptives Anabolic steroids Anabolic steroids Danazol
Non-alcoholic steatohepatitis	Amiodarone; tamoxifen
Phospholipidosis (Drug-induced phospholipidosis is characterized by intracellular accumulation of phospholipids with lamellar bodies, most likely from an impaired phospholipid metabolism of the lysosome)[46]	Amiodarone
Vascular lesions	
- Budd-Chiari syndrome (Hepatic venous outflow obstruction may develop at the level of the hepatic venules)	Oral contraceptives Anabolic steroids, azathioprine, oral contraceptives
- peliosis hepatis (Blood-filled cysts, characteristic of peliosis hepatis, developed within hepatic parenchyma)	Retinol (vitamin A), high-dose oxymetholone or fluoxymesterone therapy[49]
veno-occlusive disease	Busulfan; cyclophosphamide

Cholestasis(drugs or infectious, autoimmune, metabolic, or genetic disorders affects the formation of bile acid results in the syndrome commonly known as cholestasis)/mixed	Immune-mediated- ACE inhibitors amitriptyline, amoxicillin/clavulanic acid, carbamazepine, chlorpromazine, cotrimoxazole (trimethoprim/ sulfamethoxazole), erythromycins, phenobarbital, sulfonamides, sulindac, tricyclic antidepressants
	Non-immune-mediated Anabolic steroids, azathioprine, ciclosporin (cyclosporine), estrogens, oral contraceptives, terbinafine

Table3: Other Manifestations of drug-induced liver injury.

Autoimmune-like DILI

Drugs, such as methyldopa, minocycline and nitrofurantoin, Clometacin, Statins and biologics include Infliximab, Adalimumab, Efalimumab, Etanercept can also cause an autoimmune form of liver injury. AIH (Autoimmune Hepatitis) is characterised by the following core clinical features raised aminotransferases hypergammalobulinemia and raised immunoglobulin G female gender preponderance high titres of a variety of autoantibodies immunogenetic background; good response to immunosuppressive treatment and the presence of extrahepatic autoimmune manifestations. Detection of antibodieclusively include The detection of autoantibodies such as ANA (anti-nuclear antibodies) anti-SMA (antibodies directed against smooth muscle antigen), anti-LKM (antibodies directed against liver-kidney microsomes) anti-SLA/LP (antibodies directed against soluble liver antigen/liver-pancreas antigen) and/or anti-LC1 (antibodies directed against liver cytosol) supports the diagnosis of AIH. Because presence of high level of transaminases and IgG/gammaglobulins the aim of AIH treatment is complete normalization of transaminases and IgG/gammaglobulins, both of which are relatively good surrogate markers for the absence of intrahepatic inflammation. Drugs of similar structure or function as well as completely unrelated drugs may overlapp in causing autoimmune DILI.

Conclusion

Taking medication for small illness to chronic dissorders is very common but simmutaneously we must be conscious of these things that drugs being foreign particle/Xenobiotic to the body it has capacity to disturb normal homeostasis. DILI severity diffrers according to its drug dose and duration. So we must have that optimum knowledge regarding the at micro-level how drugs are interacting with biological system and if time and duration is deviated how it will adversely react with body to cause deteriorable consequences.in this review we tried to give thorough understanding regarding drugs or metabolite are injurious to liver when dose, duration, host related and drug related factor acts synergisticaly to cause injury to liver.So drug use for small illness or acute infections shouldt leads to generation of liver related abnormility.

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