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Interleukins mediated therapies in liver diseases and effect of comorbidity

Bouare N *et al*. Interleukins in comorbid liver diseases

Abstract
Cytokines like interleukins (ILs) play an important role in inflammation and immune innate. Yang M *et al*. carried out an interesting study related to ILs and hepatic diseases. They described the role of ILs in the pathogenesis and resolution of hepatic disorders. The authors summarized alcohol-related liver disease and virus infection-induced hepatitis, as far as clinical studies *a fortiori* carried out on IL-mediated treatments pertaining to these dysfunctions. This editorial contributive work carries upon Yang M *et al*. Review paper entitled : "Interleukins in liver disease treatment", with a main focus on therapies mediated by interleukins in comorbid liver diseases, thus exploring comorbidity influence upon IL-mediated therapy in patient with liver disorders. The documentary search concerned recent- and pertinent- data obtained from databases such as Google Scholar and PubMed.

Key Words: Cytokines; Interleukins; Liver diseases; therapy; comorbidity

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Core Tip: IL-mediated monotherapy and synergistic treatment experiments are certainly interesting for research progress. Overcoming clinical trials challenges a fortiori linked to the liver- comorbid condition, new drugs development models are being experienced,

such as dissecting the molecular subphenotypes which favour disease progression, promoting the precision medicine through multi-omics analysis, and promoting the safe, long-lasting and effective antiviral formulations. However, a judicious exploitation of newly available literature data, and applying related-useful findings pertaining to comorbidity pathway and multidisciplinary approach, should efficiently address liver diseases management in a shortwhile a fortiori to avoid long-term complications.

INTRODUCTION

The cytokines (interleukins, interferons, hematopoietic growth factors, lymphokines, monokines, and chemokines) play an important role in inflammatory and immune innate response. They are characterized by their name or abbreviation, promotor- or source- cell, main biological actions, and references from recent literatures[1]. Among them there is a group of proteins like interleukins (ILs) that participate in cellular and tissular bioreactions, binding to high-affinity receptors in cell surface[2]. ILs can play pro-inflammatory and anti-inflammatory roles, as well as paracrine and autocrine functions. ILs-primary function is to modulate both inflammatory processes (growth, differentiation, and activation) and immune innate response. As for the literature, ILs account for fourty kind of proteins ranging from 1 to 40. They are produced by various body's cells, though early thought to be expressed by the leukocytes alone[2]. Immunoassays and bioassays using antisera and antibodies allowed the discovery of new cytokines such as IL-1, -6 and -8[3]. Yang M *et al.*[4] make an interesting work pertaining to ILs and liver diseases. They reported the role of ILs in pathogenesis and resolution of hepatic disorders. The authors summarized alcohol and virus infection-induced hepatitis, since clinical studies *a fortiori* carried out on IL-mediated therapies pertaining to these liver dysfuntions. They suggested pre-clinical and clinical studies to evaluate IL-mediated monotherapy and synergistic therapies.

This editorial work contributes to Yang M *et al.* Review paper entitled : "Interleukins in liver disease treatment"; and mainly focuses on ILs-mediated therapies in patients with both liver disorders and potential comorbidities, to explore possible impact of liver

disease comorbidity on ILs-mediated therapy in patients with hepatic diseases. The bibliographic search especially carried out on recent- and pertinent- literature data, mainly obtained from Google scholar and PubMed databases.

LIVER DISEASES AND MAIN COMORBIDITIES AND CONDITIONS

A meta-analysis study estimated that 30% of people affected by non-alcoholic fatty liver disease (NAFLD) worldwide. Globally an estimated incidence rate of 4,613 new cases per 100,000 person-years reported. The variables (sex male, overweight, and obesity) were significantly associated to NAFLD[5]. As for this liver dysfunction, there was a significant difference between the study subjects regarding the sex, BMI, geographic milieu, and time-period. NAFLD shares common cardiometabolic risk factors with chronic kidney disease (CKD), including metabolic syndrome (MetS), insulin resistance (IR), type 2 diabete mellitus (T2DM)[6]. Another meta-analysis work reported a significant association of the metabolic dysfunction-associated fatty liver disease (MAFLD) with the risk of CKD[7].

The hyperglycemia- and hyperinsulinemia- condition increase *de novo* lipogenesis by stimulating lipogenic enzymes induced by the link of protein-1c to steroid regulatory element; as a result an increased endogenous production of triglycerides occurs[8]. A similar effect is obtained in case of a reduced lipolysis in adipose tissue (AT) during IR, increasing the influx of fatty acids to the liver[8]. Reciprocly hepatic steatosis may alter hepatokine secretion, modifying fatty acid metabolism as well as IR in a variety of tissues, including skeletal muscle, AT, and liver. IR is reported as being the basis of MAFLD development process, abnormal metabolic profile in patients, and disease complications; although more comprehensive studies are required to understand and test this hypothesis as well as others which may develop[8]. Adiponectin ensures the regulation of body carbohydrate metabolism, as well as insulin homeostasis, fatty acid oxidation (FAO) and hepatic sensitivity to insulin through phosphorylation and activation of AMP-dependent protein kinase (AMPK)[9]. As for obesity, a large amount of free fatty acids enters in the liver *via* the hepatic portal pathway[9].

Metabolic disorders can be defined by the conditions and level of biomarkers, such as visceral obesity, hypertension (HTA), IR, hyperglycemia, hypertriglyceridemia, and decreased high-density lipoprotein (HDL). The occurrence of three among those abnormalities may characterize a MetS[10]. NAFLD is a liver manifestation of metabolic syndrome; this hepatic abnormality can progress to non-alcoholic hepatic steatosis (NASH), defined as a macrovesicular accumulation of triglycerides (TG) in liver cells[9, 10]. NASH can progress to CVD, T2DM, and CKD; it may even evolve toward HCC without cirrhosis episode. HCV infection and NASH have been reported to significantly impact on the public health worlwide. Some diets (including saturated and trans fats, sodium, refined- and processed- sugar) promoting pro-inflammatory cytokines are associated with high incidence of MetS. The uptake of phenolic acids diets (fruits, vegetables, nuts, green tea, and coffee) have been shown reducing the prevalence of IR, NAFLD and fibrosis. Whereas NASH treatment can be complicated by the comorbidities of T2DM and CVD, physical activity may slow NAFLD and NASH progression and severity. Appropiate lifestyle (including food hygien and quality, and exercise) is an essential first-line therapy for both NASH and CVD[10, 11]. Aspirin is recommended for CVD's secondary prevention, but not for NASH owing the limited- available data. Statins are recommended in patients with conditions such as : hyperlipidemia, T2DM, 10-years atherosclerotic cardiovascular disease (ASCVD) risk, or CVD's clinical state. Statins are also suggested safe in NAFLD/NASH, exept its prescribing in patients with Child–Pugh B/C cirrhosis and Model for End-Stage Liver disease (MELD) score over 15, requiring multidisciplinary risk-to-benefit evaluation by avoiding the toxic outcomes such as myositis and liver failure[10].

Yang M *et al.*,[4] reported the role of IL-12 family in immune response regulation and naïve T cell's differentiation in diverse pathologies, including inflammatory-, autoimmune-, and cardiovascular- diseases. This IL-12 family, especially IL-12 and 27, were described able to inhibit chronic HBV and HCV infections, respectively[12]. Furthermore, an animal model study (IL-12p40-deficient mice infected by human metapneumovirus (hMPV)) reported IL-12 function in reducing lung inflammation and

mucus secretion[12]. That experimental mice with hMPV infection progressively experienced abnormal lung functions and altered cytokine response. The authors highlighted the importance of immune-modulation of IL-12 family in viral infections, which helps reducing virus replication and regulating virus-induced inflammation. However, authors suggest to investigate the involvement of cytokines in the host's antiviral defense. They propose further research to understand with precision their mechanism of action targeting viral infections, since long-lasting anti-inflammatory responses and persistent pro-inflammatory course may not beneficial for the infected subjects. In addition, an imbalanced immune response may trigger irreversible tissue injury and organ failure, or delayed virus clearance. They concluded the challenging perspective for developing cytokines into effective antiviral therapies, which requires rigorous research fulfilling conditions, such as safe, long-lasting and effective drugs formulations for viral diseases.

Variants of the IFN-λ3 (IL-28B) gene were often described as responsible for the clinical progression of various pathologies[13].

The 'cytokine storm', as release of pro-inflammatory cytokines (including ILs), leads to molecular pathophysiology defect and possible organ damage into the lung, heart, or liver. Potential liver injury in COVID-19 patients has been reported, as shown by the levels of laboratory parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and albumin[14].

COVID-19 has been described to be involved in diverse body systems and organs failure. Alongside respiratory tract defect, potential damages reported pertaining to gastrointestinal tract, liver and kidney organs, immune and neurological systems. Other disorders may occur including coagulation defetcs and cutaneous symptoms. The risk of COVID-19 morbidity and mortality increased in patients with specific comorbidities such as obesity, diabetes, and hypertension[15]. As for COVID-19 in patients with pre-existing chronic liver disease (CLD), apart from above specific comorbidities, predictors such as CLD severity, or related etiology, and COVID-19 severity, with breathless may lead to mortality[16]. However, authors suggested comprehensive relationship research

between these risk factors and outcomes. As far as the COVID-19 pandemic is concerned, patients with fatty liver disorders (FLD) had a high risk to being infected, whereas FLD incidence increased in containment periods[17]. These patients experienced proven risk factors associated with the severity of infection, such as BMI, metabolic comorbidities, and liver fibrosis though FLD *per se* considered as doubtful independant risk factor.

High risk of liver defect reported in MAFLD patients who were infected by SARS-CoV-2. Monitoring of markers pertaining to heart, kidney and liver function, muscle injury, and coagulation required in patients with COVID-19. Owing common polytherapy in COVID-19, such patients may experience drug induced liver injury (DILI)[18].

Silaghi *et al.*,[19] reported a decrease in insulin secretion (due to a reduced beta cells granules secreting insulin) were observed in patients with COVID-19. SARS-CoV-2 may alter beta cells into the pancrea and trigger the production of pro-inflammatory cytokines. In the AT, pro-inflammatory processes leading to persistent low-grade inflammation involved in T2DM occurrence and IR pathogenesis. Hyperglycemia and IR reported in COVID-19 patients without any diabete story. Apoptosis in SARS-CoV-2-induced thyroid lesions also reported[19]. A decrease for blood plasma levels in antioxidant enzymes such as glutathione peroxidase (GPx), glutathione (GSH), superoxide dismutase (SOD), and catalase was observed in patients with COVID-19, in addition to the rise of oxidative stress parameters, which increases severity- and mortality- risk of disease. That oxidative stress influenced by inflammatory cytokines production, innate immune response activation, or infected cells death. Likewise a reduction of GSH rates due to factors, such as dehydration, malnutrition, high urea levels and diarrhea, and increasing cyanate rates experienced in COVID-19 may trigger the cataractogenesis.

Acute liver failure (ALF) and CLD associated with diverse neurological alterations. Brain inflammation involved in neurological disorders among patients with hepatic encephalopathy (HE) documented. The gut microbiota dysbiosis, accompanied by intestinal permeability impairment, triggers bacterial translocation and endotoxemia, causing systemic inflammation such neuroinflammation in brain tissue[20]. Furthermore, metabolites from gut microbiota may alter central nervous system (CNS) leading to

neurological complicated state, with clinical manifestations worsening. However, factors, including the etiology, comorbidity, disease severity, and external milieu may influence neuroinflammation as well as gut microbiota. Hence the neuroinflammation may be promising for HE management. The available therapeutic options are effective to a degree, and new useful approaches with clinical practice implications are suggested[20].

Osteopenia and osteoporosis pathogenesis (field NAFLD) remain less studied. A high prevalence of NAFLD reported in patients with obesity, which may lead to sarcopenia regardless patient's age. Authors hypothesized a possible occurrence of osteopenia and osteoporosis in these patients, since metabolism, biological function and skeletal muscle are closely linked to bone health. They suggest further research pertaining to osteopenia, osteoporosis, and sarcopenia in NAFLD[21].

The link between heart disease and iron abnormal levels (low- and over- load) is reported[22]. Systemic iron metabolism is regulated by Hepcidin that is induced by IL-6. Hepcidin belongs to the acute phase proteins released by the liver in response to an inflammatory state. In an inflammatory course, homeostasis of systemic iron is dysregulated, which may lead to low blood iron level[22]. Authors concluded that the underlying mechanisms of iron handling and inflammatory processes are linked; these processes occur in the cardiovascular system and particularly in heart disease. Iron handling in cardiomyocytes is enough well understood, but little information is known regarding the heart barrier and its response to systemic iron. They suggested comprehensive research to better understand the interactions between systemic- and cardiac- iron metabolism. Thus drugs targeting iron may be a promizing way to prevent and treat inflammatory processs leading to cardiovascular disease disorders or complication.

The link between psoriasis and a high risk of NAFLD reported. The screening of NAFLD and its comorbidities is recommended for all patients with psoriasis. Authors suggested prospective controlled experiments to assess the effectiveness of biological treatments in preventing NAFLD evolvement in these patients[23].

NAFLD and alcohol-related liver disease (ALD) reported to sharing characteristics regarding the pathophysiology-, histology- and genetic- of disease. In addition alcohol and metabolic dysfunction reported as coexisting etiological factors among patients with hepatic steatosis[24]. In patients with fatty liver disease, authors have suggested to assess both causality factors such as MetS and alcohol consumption, which applies a better prognosis and personalized medicine approach.

To categorize steatotic liver patients, it is suggested to consider cardiometabolic risk factors. Moreover, a mixed subtype, metabolic dysfunction-associated steatotic liver disease (MASLD) combined with a high alcohol intake (MetALD), throws the light on patients with moderate or high alcohol intake who were ignored. However, this new nomenclature does not precise the contribution of metabolic dysfunction and alcohol intake to the development and evolvement of SLD[25].

Fibrosis may be defined as a fibrous connective tissues increase and decreased parenchymal cells in organs or tissues including lung, heart, liver, kidney, and skin. Long-term fibrosis process may trigger organ and tissue dysfunction and subsequent failure. IL-1 family of cytokines are involved in the occurrence and progression of diverse fibrotic diseases; consequently their biology, association with diseases and clinical application attracted scientists curiousity in many countries[26]. As for IL-1 family, 11 cytokines and 10 receptors identified[26]. IL-33, described as a cytokine with higher pro-fibrotic potency of the IL-1 family, is involved in the occurrence and progression of diverse fibrotic pathophysiologies. Therefore hampering its signaling pathway may decrease fibrosis level, based on animal models experiment. However, the clinical application of its specific- neutralizing antibody or specific- receptor ST2 inhibitor remains to be confirmed. Some researchers have questioned the possibility for clinician to directly apply IL-1Ra and IL-37-related drugs as treatment. Further studies focused on comprehensive signaling pathways, regulatory mechanisms, and medicine targets are needed regarding fibrotic diseases therapy. In terms of research on the IL-1 family, the contribution of basic research (field drug development) would be valuable. A thorough

understanding of the roles and mechanisms of IL-1 family members should enable the development of more effective drugs to prevent and treat fibrotic diseases[26].

Autoimmune liver diseases consisting of different types of chronic disorders such as autoimmune hepatitis, and the primitive form of biliary cholangitis and sclerosing cholangitis. The patients with liver cirrhosis and NAFLD may experience glucose disturbances such IR and are at high risk to develop diabetes. Despite scarce reported evidence pertaining to glucose disturbances among patients with autoimmune liver disease, there is a potential trend towards a great risk of type 1 diabetes (T1DM) and T2DM[27]. Although there are unknown underlying mechanisms, a few attempts at explanation are reported like genetic predisposition, concurrent NAFLD or cirrhosis, and steroid therapy leading to glucose homeostasis impairment. Hence improving awareness and surveillance of diabete occurence in patients affected by autoimmune liver disorder may be interesting. The existing guidelines for diabetes management may serve, apart from in patients experiencing advanced hepatic cirrhosis in which HbA1c may be unreliable marker, and an insulinotherapy *a fortiori* recommended. Sodium–glucose cotransporter 2 (SGLT) inhibitors suggested, as a useful treatment of refractory ascites, is reported[27].

Much evidence reported upon cross-linkages contribution of metabolic abnormalities and innate immune system regarding occurrence and evolvement of NAFLD[28]. A better understanding of these bidirectional links should highly improve patients' management. Furthermore, lipid metabolic abnormalities and innate immune system connect NAFLD to atherosclerosis, showing a high clinical interest[28].

Liver diseases comorbidity, risk factors and related pathobiology or pathophysiology are summarized (Table 1).

COMORBIDITY IMPACT ON INTERLEUKINS-MEDIATED THERAPY IN LIVER DISEASES

Comorbid pathologies including (obesity, T2DM, CVD) can trigger hepatic disorders, which makes liver diseases management with conventional medicines challenging. In addition, unsafe prescribing, polytherapy, misuse or overuse of drug and adverse drug

reactions (ADRs) may further complicate the management[29]. Many harmful cytokines production, including IL-1β, tumor necrosis factors (TNF-α), nuclear factor (NF) κB, activator protein (AP-1), macrophage inflammatory protein (MIP), toll-like receptor (TLR4), are assessed for clinical significance owing a complicated liver state, based evidence recommendation. Liver fibrosis mediators, such as the transforming growth factors (TGF) β, matrix metalloproteinases, and extracellular matrix (ECM), were even identified as interesting targets[29]. Recent investigations have shown the multiple benefits of polyphenol-based therapy, as these molecules have protective effects on cellular components such as membrane, cytoplasm, and genetic materials. Since there is no effective treatment against fibrosis yet, daily consumption of citrus polyphenols can be an effective alternative. Pharmacological data from citrus fruits have shown that these fruits are extremely effective and well tolerated. Hence citrus-derivative polyphenols are recommended for preventing multiple chronic diseases. Numerous powerful components were isolated such as caffeic acid, naringenin, and limoline, which have shown highly effective. Large-scale clinical trials are required to determine the accurate therapeutic dose of these components for designing the next-generation drugs. Large-scale effective trials can elucidate a powerful drug molecule from citrus fruits[29].

As for cytokines, since long-lasting anti-inflammatory responses and persistent pro-inflammatory course may not beneficial for infected patients, their implication in the host's antiviral defense is questionned[12]. Consequently, further research is required for accurate understanding of their mecanisms of actions in targeting viral infections. Hence the challenging perspective for developing cytokines into effective antiviral therapies, which requires rigorous research to ensure some a conditions (including safe, long-lasting and effective antiviral formulations).

Regarding COVID-19, both genetic polymorphisms rs12979860 and rs1298275 of IL-28B were frequently described as unfavorable for pathologies such as hepatitis C and HCC. The great genetic variability of HLA reported as a crucial factor relevant to the late immune response, owing its ability to recognize antigens, with HLA-B*46:01 SNP being linked to the COVID-19 susceptibility. IL-6, rs1554606 showed a strong relationship with

COVID-19 clinical progression, whilst rs2069837 was identified as capable of protecting the host against this infection[13].

The 'cytokine wave' may occur in COVID-19, leading to molecular pathophysiology state with possible multiorgans failure[14, 19]. Potential liver injury in COVID-19 patients were reported, as shown by the levels of hepatic laboratory parameters, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and albumin[14]. We know liver implication in protein synthesis, and drug metabolism through cytochrome P450 (CYP); consequently a minor alteration in liver function may extremely affect the hepatic clearance of xenobiotics (or chemical exposure of an organism). It is established that the high cytokine levels are common in COVID-19 patients. Likewise in patients with non-SARS-CoV-2 virus infection, literature data showed a suppression of CYP enzymes in an infection-related cytokine increase and inflammation course[13]. Beside the interventional COVID-19 drugs uptake, patients may be under a therapeutic regimen for comorbidities. Observational studies have shown that patients with HTA, hyperglycemia or obesity are more susceptible to COVID-19. This rises the drugs- and diseases- interaction issue in patients, since interventional drugs (for instance remdesivir and dexamethasone) and agents against comorbidities may be affected by a compromised CYP-mediated liver metabolism. Therefore the caregivers should pay attention to COVID-19 about CYP-driven drug metabolism interaction in managing patients either by adjusting drugs dose or make discontinuation as appropriate[14].

Regarding less ADRs or interactions and because a cost-saving option, alternative medicine (traditional therapy) is being acknowledged[29]. A seasonal fruit (citrus), known for its great medicinal value is widespread worldwide. That fruit has diverse biological activities due to its chemical components such as: polyphenols, flavonols, carbohydrates, amino acids, and oils. Polyphenol-based molecules highly proved effective against inflammatory cytokines and profibrogenic factors producing. These chemical molecules may prevent free radicals formation as well as oxidative stress occurrence. Moreover, polyphenols triggered induction of useful functional proteins and

mitochondrial biogenesis from protective genes, including AMPK, superoxide dismutase, catalase and heme oxygenase (HO).

Psoriasis shares with NAFLD diverse pathophysiological events such as systemic inflammation and IR. Hence preventing or altering systemic inflammatory process may be useful in reducing NAFLD progression or improving it[30].

While Western diet may affect gut permeability and its microbiota component and function, leading to the pathobionts selection, Mediterranean diet reinforces health-beneficial microbiota, impacting positively on lipid and glucose metabolism and the hepatic inflammatory process[31]. Using antibiotics and probiotics improved NAFLD characteristics with mitigated results. Furthermore, NAFLD-associated comorbidities medications may modulate the gut microbiota. Medicines used to treat T2DM like metformin, glucagon-like peptide-1 (GLP-1) agonists, as well as SGLT inhibitors, are beneficial for several reasons : effective regulation of glucose homeostasis, reduction of liver fat content and inflammation, and change in intestinal microbiota component towards a healthy profile. Bariatric surgery reported to make changes in the gut microbiota, which impact gastrointestinal anatomy and improve NAFLD histological state. Further research pertaining to fecal microbial transplantation (FMT) and next-generation probiotics is being experienced as the new NAFLD therapeutic tools[31].

Lactobacillus acidophilus (L. acidophilus) KLDS1.0901 reported contributing for high fat diet (HFD)-induced NAFLD therapy, which allowed liver features improvement and microbiota component modulation. Hence this bacteria may be a candidate for NAFLD treatment optimization[32]. L. acidophilus KLDS1.0901 uptake reduced IL-6, IL-1β, and TNF-α levels with an increase in IL-10 concentration, according to an animal model study. This administration could improve the gut barrier function, upregulating mRNA expression levels of some molecules such as occludin, claudin-1, ZO-1, and Muc-2, whilst decreasing the levels of lipopolysaccharide (LPS) and D-lactic acid. Furthermore, the L. acidophilus KLDS1.0901 uptake modulated intestinal microbiota towards the normal profile. The authors suggested that L. acidophilus KLDS1.0901 may be a useful candidate to improve NAFLD[32].

Pomegranate (*Punica granatum*) reputed as a functional food with diverse beneficial properties and effects upon the health. Jafarirad *et al.*[33] reported that pomegranate extract decreased significantly the levels of markers, such as ALT, AST, gamma glutamate transferase (GGT), fetuin-A, fibroblast growth factor 21 (FGF-21) and IL-6 among patients with NAFLD, as compared to a placebo group. Pomegranate may be a useful supplemental therapy, since its extract experienced to have an improved effect on the majority of these related-NAFLD laboratory parameters[33]. While this medicinal extract led to a rise in total antioxidant capacity, it did not show any effect on alkalin phosphatase (ALP), according to that study's findings. That study showed that a daily intake of 450 mg of pomegranate extract (i.e., two tablets, standardized on the basis of 40% ellagic acid) for 12 wk reduced hepatic enzymes, hepatokins and IL-6 and thus increased total antioxidant power[33].

SGLT2 inhibitors reported to play a beneficial role in preventing hospitalization for decompensated cardiac failure and protecting kiddney; which limits a deterioration state of glomerular filtration, in patient presenting or not the diabete mellitus[34]. These medicines reported to prevent the occurrence of atherosclerotic cardiovascular state and death caused by cardiovascular event in patients with concomittent diabete and cardiovascular disorder. We know that patients with T2DM may have a high associated comorbidities burden such as HTA, dyslipidemia, hyperuricemia, obesity, NAFLD, polycystic ovary syndrome (PCOS), vascular aging, breath disorders, and osteoporosis. An integrated and pluralistic approaches should be applied for the management of these patients. The authors suggested further studies to corroborate SGLT2 inhibitors effectiveness in non-diabetic disorders such as hyperlipemia, PCOS or vascular aging[34].

The hepatic inflammatory- and fibrosis- processes are trigerred by the activation of liver-resident macrophages (or Kupffer cells). Owing macrophages plasticity, these cells may be polarized into various phenotypes using different microenvironmental stimuli[35]. That polarization of macrophages into phenotypes like M1 (with pro-inflammatory property) or M2 (with anti-inflammatory effect) regulated by complex cell-signaling profiles such us PI3 Kinase (PI3K)/Akt pathway. It is demonstrated that inhibiting M1-

type or promoting M2-type polarization may be effective therapy against CLD (including ALD, NAFLD, and hepatic fibrosis). This cell-signaling pathway may act as a potential modulator of the macrophage-related events such as survival, migration, proliferation, and responses to metabolism- and inflammatory- signals. The anti-inflammatory cytokine expression induced by PI3K/Akt pathway activation, promoting M2-like phenotype; which facilitates the tissue repair and inflammation resolution. Conversely, inhibiting the PI3K/Akt signaling could rise M1-like phenotype, which increases liver impairment. Plant chemicals may be used to effectively treat CLD, as future liver disease therapy, targeting PI3K/Akt pathway for regulating the polarization of macrophage and its activity[35].

There are notable differences between patients with NASH in terms of associated comorbidities, their severity, and the level of control achieved by different drugs. These comorbidities in addition to their management constitute an important source of heterogeneity between the trial participants; this inevitably impacts the evaluation of aspects such as trial outcomes, adverse events and patient compliance, as well as the applicability of results in the real-world context[36]. Moreover, these participants may also experience changes in the status of these comorbidities over the course of trial, as some trials can last for years. Hence for the management of the comorbidities a guidance that defines acceptable limits was proposed by the liver forum regarding management of comorbidities in non-alcoholic steatohepatitis therapeutic trials. In fact, this guidance is intended to be compatible not only with the specifics of NASH that is a multisystemic disease but also with trial concerns including feasibility and integrity. It should be updated, as concepts, treatments and standard of care are evolutive in space and time[36]. NAFLD characteristics may overlap with those of metabolic syndrome diseases; which combined with the heterogeneity of disease mechanisms, may complicate the diagnosis and prognosis of this liver disorder, and hinder research progress for biomarker and drug discoveries. Pirola et Sookoian[37] explored the heterogeneous clinical pattern of NAFLD by cluster analysis of molecular markers that serve as an approximation for the stratification of disease into molecular subtypes. The authors reported unique biological

pathway pertaining to each clinical subtype/group, such as NAFLD and obesity, NAFLD and HTA, NAFLD and dyslipidemia, and NAFLD and T2DM. Therefore, a better understanding of disease for biological perspective can improve the management of patients with NAFLD, which requires dissecting molecular subphenotypes responsible for disease progression[37].

The increasing socioeconomic burden for ALD was reported worldwide, whilst its frequence underrated and patients with ALD rarely diagnosed in an earlier stage of the disease[38]. Alcoholic hepatitis (AH) is a distinct syndrome that occurs in the form of syndromic systemic inflammation with life-threatening clinical signs. ALD spectrum ranges from steatosis, fibrosis, and cirrhosis to HCC pertaining to chronic alcohol consumption over 20 g/day in women and over 30 g/day in men. ALD is a clinical syndrome of progressive icterus occurring in patients who excede the normal day dose of alcohol intake. These patients may present or not the signs of ascites or HE. In the case of severe AH, prednisolone indicated as first-line therapy, whilst possible various complications may occur[38]. Whether prednisolone treatment fails, early-stage liver transplantation can be a useful option for highly selected patients. Furthermore, abstinence is the cornerstone of long-lasting care, even if relapse is mostly registered in patients. Emerging treatment options focus on main targeting approaches such as the liver inflammation prevention, oxidative stress decrease, gut dysbiosis improvement, and increase in hepatic regeneration. The promotion of precision medicine through multi-omics analysis and consideration of the gender is justified to overcome the challenges and obstacles to conducting successful clinical trials in patients with ALD[38]. Patients may experience both life-threatening clinical states like acute liver failure (ALF) and acute-on-chronic liver failure (ACLF). Whereas ALF characterized by a liver dysfunction of rapid evolution, coagulopathy and HE among patients without CLD, ACLF occurs in patients with prior CLD[39]. These both deadly diseases may drive to diverse organs failure and precoce mortality. A cytokine (IL-22) is produced by immune cells, and especially it targets epithelial cells like hepatocytes. Preclinical models and clinical trials including alcohol-associated hepatitis (AH) reported the protective effect of

IL-22 against organ damage and bacterial infection reducing. The hepatoprotective effect and immune-modulating capacity of IL-22 experienced in preclinical models for ALF and ACLF; in addition to positive results provided by the clinical trials for other liver and inflammatory diseases, especially AH; which allows to postulate a positive prediction about efficacy of IL-22[39].

Although liver transplant (LT) outomes improved sensibly in the recent years, long-term morbidity and death remain noticeable[40]. Graft function and comorbidities, including complications of metabolic syndrome, are not responsible for the majority of late deaths. However, late issues seem to be linked to *de novo* neoplasms in LT recipients. In the other hand, a long-term strategy for LT recipients management by drug toxicity reducing, high-risk patients identification, and multidisciplinary team collaborating may further increase the survival rate after LT[40].

The liver injury may be triggered by an inflammatory and innate immune response, which leads to Kupffer cells activation. That liver-specific cells activation allows the release of multiple cytokines, including IL-6, IL-1ß, and TNFα[41]. A liver-related co-mitogen, as the anhancer of liver regeneration (ALR) reported to have antioxidative and anti-apoptotic properties, in addition to a reducing effect upon experimental NAFLD and cholestasis. Moreover, patients with NAFLD or cholestasis experienced a decreased expression for ALR, though the underlining mecanisms of its regulation (under these conditions) are less known. Furthermore, IL-1ß therapy reduced ALR promoter activity, mRNA and protein expression. IL-1ß has induced early growth response protein-1 (Egr-1), an ALR inducer, without activate the expression of ALR. That IL-1ß relared property may be explained by an Egr-1 binding defect to the ALR promoter[41]. Moreover IL-1ß reduced the expression and nuclear localisation of hepatocyte nuclear factor 4 α (HNF4α), another factor inducing ALR transcription. Importantly, c-Jun, a factor of transcription and potential regulator of ALR and HNF4α, has shown an increased nuclear phosphorylation level from IL-1ß therapy. However, ALR or HNF4α expression had not been changed by c-Jun. The authors reported evidence pertaining to IL-1ß regulation of anti-apoptotic and antioxidative ALR *via* a reduced Egr-1 promoter binding and

decreased HNF4α expression independent of c-Jun activation[41]. They hypothesized low ALR tissue levels in NAFLD and cholestatic liver injury may be due to IL-1ß, contributing to disease progression. As for IL-1 inhibitors, the rare clinical experiments do not allow to elucidate their beneficial role in NAFLD therapy, even if preclinical investigations are promising[42]. Moreover, the mostly evidences reported pertaining to the treatment by IL-1 family members are from preclinical experiments. Owing the lack of clinical data and difficulty of access, the way is still long to achieve beneficial result from IL-1 family members in clinical practice[43].

Hepatocellular death involves a fundamental biological process that regulates the progression of liver disease *via* distinct mechanisms. Much evidence reported the implication of IL-1 family in liver cell apoptosis[44]. Promoting new and innovative management approaches pertaining to liver diseases, through close collaboration between fundamental and clinical scientists, should be a comprehensive way to understand the complex processes regarding IL-1 family cytokines' contributions in hepatocellular apoptosis[44].

Alternanthera brasiliana L. is a flowering plant in the Amaranthaceae family that is popularly known under the name "penicillin". It is used in traditional medicine for its beneficial effects against infections, coughs, inflammatory diseases, as well as its wound healing properties[45]. The *Alternanthera brasiliana L.* (AB) hepatoprotective effect can be attributed to the high terpenoid content, which attenuates liver damage and the related fibrotic changes through modulation of matrix metalloproteinases (MMPs), nuclear factor-κB (NF-κB) (p65) and transforming growth factor-β axis (TGF-β/Smad)[45].

CONCLUSION

Many common cardiometabolic risk factors reported about NAFLD and CKD, such as MetS, IR, T2DM, uricemia, dyslipidemia, abdominal obesity, proinflammatory milieu, hypoadiponectin, and prothrombotic-hypofibrinolytic state. MAFLD reported significantly associated with the risk of CKD. Patients with T2DM may have several comorbidities or conditions, including HTA, dyslipidemia, hyperuricemia, obesity,

NAFLD, polycystic ovary syndrome (PCOS), vascular aging, breath disorders, and osteoporosis. Therefore, applying an integrated and pluralistic approach should be a better option for managing these patients. The comorbidities and their management, as an important source of heterogeneity between the trial participants, can really impact the trial evaluation regarding the outcomes, adverse events and patient compliance, and trial results applicability in the real-world context.

The comorbid pathologies may be responsible for liver disorders, which makes challenging the treatment of hepatic diseases with conventional drugs. Moreover, unsafe prescribing, polytherapy, inadequate use of drug, and adverse drug reactions ADRs may complicate the management. Numerous harmful cytokines production, such as IL-1β, TNFα, NFκB, AP1, MIP, TLR4, are assessed for clinical significance, owing a complicated liver state.

There is an unique biological pathways pertaining to each clinical subtype/group, such as NAFLD and obesity, NAFLD and HTA, NAFLD and dyslipidemia, and NAFLD and T2DM.

IL-22 reported to have a hepatoprotective and immune-modulating effect upon both ALF and ACLF, in addition to its positive results shown by the clinical trials for other liver- and inflammatory- diseases, such as AH.

Conducting IL-mediated monotherapy and synergistic treatment experiment may be insightful for science progress and new drugs development. Alongside, a judicious exploitation of newly available literature data pertaining to the comorbidity and multidisciplinary approach should efficiently address liver diseases management in a shortwhile, and to prevent especially long-term complications.

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