ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2024 July 27; 16(7): 973-1069

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (ESCI), Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJH* as 2.5; JIF Quartile: Q2. The *WJH*'s CiteScore for 2023 is 4.1 and Scopus CiteScore rank 2023: Hepatology is 41/82.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

PUBLICATION DATE
July 27, 2024

PUBLISHING PARTNER
Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

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https://www.wjgnet.com/bpg/gerinfo/242

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https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html

World Journal of Hepatology

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World J Hepatol 2024 July 27; 16(7): 980-989

DOI: 10.4254/wjh.v16.i7.980

ISSN 1948-5182 (online)

EDITORIAL

Interleukin-mediated therapies in liver diseases and comorbidity effects

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade C

P-Reviewer: Manrai M, India

Received: February 28, 2024
Revised: May 13, 2024
Accepted: May 17, 2024
Published online: July 27, 2024
Processing time: 148 Days and 15.5 Hours

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Abstract

Cytokines like interleukins (ILs) play important roles in inflammation and innate immune. Yang and Zhang 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-induced hepatitis, as far as clinical studies *a fortiori* carried out on IL-mediated treatments pertaining to these dysfunctions. This editorial contributes to the review by Yang and Zhang titled, "Interleukins in liver disease treatment", and focuses on therapies mediated by ILs in comorbid liver diseases. The documentary search was conducted on recent pertinent literature, primarily using the Google Scholar and PubMed databases.

Key Words: Cytokines; Interleukins; Liver diseases; Therapy; Comorbidity

Core Tip: Interleukin-mediated monotherapy and synergistic treatment experiments are certainly interesting for scientific insights. 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 multiomics analysis, and promoting the safe, long-lasting and effective antiviral formulations. However, a judicious exploitation of newly available data, and applying related-useful findings pertaining to comorbidity pathway and a multidisciplinary approach, should efficiently address liver diseases management in a short-term *a fortiori* to avoid long-term complications.

Citation: Bouare N, Delwaide J. Interleukin-mediated therapies in liver diseases and comorbidity effects. *World J Hepatol* 2024; 16(7): 980-989
URL: https://www.wjgnet.com/1948-5182/full/v16/i7/980.htm
DOI: https://dx.doi.org/10.4254/wjh.v16.i7.980

INTRODUCTION

Cytokines [*e.g.*, interleukins (ILs), interferons, hematopoietic growth factors, lymphokines, monokines, and chemokines] play important roles in inflammatory and innate immune responses. They are characterized by their name or abbreviation, promoter or source cells, main biological actions, and references from the recent literature[1]. Among them, ILs participate in cellular and tissue bioreactions and bind to high-affinity cell-surface receptors[2]. ILs can play proinflammatory and anti-inflammatory roles and have paracrine and autocrine functions. The primary function of ILs is to modulate inflammatory processes (growth, differentiation, and activation) and innate immune responses. In the literature, ILs account for 40 different proteins, numbered from 1 to 40. They are produced by various cells in the body, although they had been previously thought to be expressed only by leukocytes[2]. Immunoassays and bioassays using antisera and antibodies have allowed the discovery of new cytokines such as IL-1, -6, and -8[3]. Yang and Zhang[4] reported the role of ILs in the pathogenesis and resolution of hepatic disorders and summarized alcohol- and virus-induced hepatitis based on *a fortiori* clinical studies of IL-mediated therapies pertaining to these liver dysfunctions. They suggested that preclinical and clinical studies be conducted to evaluate the efficacy of IL-mediated monotherapy and synergistic therapies.

This editorial contributes to the review by Yang and Zhang[4], titled "Interleukins in liver disease treatment" and mainly focuses on IL-mediated therapies in patients with both liver disorders and potential comorbidities. A bibliographic search was conducted on recent pertinent literature, primarily using the Google Scholar and PubMed databases.

LIVER DISEASES, COMORBIDITIES, AND CONDITIONS

A meta-analysis estimated that 30% of individuals worldwide are affected by nonalcoholic fatty liver disease (NAFLD). The global incidence has been estimated as 4613 new cases per 100000 person-years. Variables such as male sex, overweight status, and obesity have been significantly associated with NAFLD[5]. Regarding liver dysfunction, the study participants had significant differences in terms of sex, body mass index (BMI), geographic milieu, and study period. NAFLD shares common cardiometabolic risk factors with chronic kidney disease (CKD), including metabolic syndrome (MetS), insulin resistance (IR), and type 2 diabetes mellitus (T2DM)[6]. Another meta-analysis reported a significant association between metabolic dysfunction-associated fatty liver disease (MAFLD) and the risk of CKD[7].

Hyperglycemia and hyperinsulinemia increase *de novo* lipogenesis by stimulating lipogenic enzymes induced by the link between protein-1c and steroid regulatory elements, resulting in an increased endogenous production of triglycerides[8]. A similar effect is observed in the reduced lipolysis in adipose tissue (AT) during IR, which increases the influx of fatty acids into the liver[8]. Reciprocally, hepatic steatosis may alter hepatokine secretion, modifying fatty acid metabolism and IR in a variety of tissues, including skeletal muscle, AT, and liver. IR is reported to be the basis of the MAFLD development process, abnormal metabolic profiles in patients, and disease complications; however, more comprehensive studies are required to understand and test this hypothesis[8]. Adiponectin regulates carbohydrate metabolism, insulin homeostasis, fatty acid oxidation, and hepatic sensitivity to insulin through the phosphorylation and activation of AMP-dependent protein kinase (AMPK)[9]. In obese individuals, large amounts of free fatty acids enter the liver *via* the hepatic portal pathway[9].

Metabolic disorders can be defined by the condition and levels of biomarkers, such as visceral obesity, hypertension (HTA), IR, hyperglycemia, hypertriglyceridemia, and decreased high-density lipoprotein levels. The occurrence of three of these abnormalities may characterize MetS[10]. NAFLD is a liver manifestation of MetS; this hepatic abnormality can progress to nonalcoholic hepatic steatosis (NASH), defined as the macrovesicular accumulation of triglycerides (TG) in liver cells[9,10]. NASH can progress to cardiovascular disease (CVD), T2DM, and CKD and may even evolve toward hepatocellular carcinoma (HCC) without cirrhotic episodes. Hepatitis C virus (HCV) infection and NASH significantly impact public health worldwide. Some diets, including those with saturated and trans fats, sodium, and refined and processed sugar, that promote proinflammatory cytokines are associated with a high incidence of MetS. The intake of phenolic acids (*e.g.*, fruits, vegetables, nuts, green tea, and coffee) reduces the prevalence of IR, NAFLD, and fibrosis.

Although NASH treatment can be complicated by the comorbidities of T2DM and CVD, physical activity may slow the progression and severity of NAFLD and NASH. An appropriate lifestyle, including food, hygiene, quality, and exercise, is an essential first-line therapy for both NASH and CVD[10,11]. Aspirin is recommended for secondary prevention of CVD, but not NASH, owing to the limited availability of data. Statins are recommended for patients with conditions such as hyperlipidemia, T2DM, a 10-year atherosclerotic cardiovascular disease (ASCVD) risk, or a CVD clinical state. Statins are also suggested to be safe for patients with NAFLD/NASH, except for patients with Child–Pugh B/C cirrhosis and a Model for End-Stage Liver Disease score > 15, requiring multidisciplinary risk-to-benefit evaluations to avoid toxic outcomes such as myositis and liver failure[10].

Yang and Zhang[4] reported the role of the IL-12 family in immune response regulation and naïve T-cell differentiation in diverse pathologies, including inflammatory, autoimmune, and cardiovascular diseases. The IL-12 family, especially IL-12 and -27, can inhibit chronic hepatitis B virus and HCV infections, respectively[12]. Furthermore, an animal model study using IL-12p40-deficient mice infected with human metapneumovirus (hMPV) demonstrated that IL-12 reduces lung inflammation and mucus secretion[12]. Experimental mice infected with hMPV progressively experience abnormal lung function and altered cytokine responses. The authors highlighted the importance of immune modulation by the IL-12 family in viral infections, which helps reduce viral replication and regulate virus-induced inflammation. However, the authors suggested investigating the involvement of cytokines in host antiviral defense to precisely understand their mechanism of action targeting viral infections, since long-lasting anti-inflammatory responses and persistent proinflammatory courses may not be beneficial. In addition, an imbalanced immune response may trigger irreversible tissue injury, organ failure, and delayed viral clearance. Therefore, the challenge of developing cytokines into effective antiviral therapies requires rigorous research to provide as safe, long-lasting, and effective drug formulations for viral diseases.

IFN-λ3 (IL-28B) gene variants are responsible for the clinical progression of various pathologies[13]. The 'cytokine storm, *i.e.*, the release of proinflammatory cytokines, including ILs, leads to molecular pathophysiological defects and possible organ damage to the lung, heart, or liver. Potential liver injury in patients with coronavirus disease 2019 (COVID-19) has been reported, as indicated by the levels of laboratory parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and albumin[14].

COVID-19 has been associated with diverse systemic and organ failures. Alongside respiratory tract defects, potential damage to the gastrointestinal tract, liver, kidneys, and immune and neurological systems has been reported. Other disorders, such as coagulation defects and cutaneous symptoms, may also occur. The risk of COVID-19 morbidity and mortality increases in patients with specific comorbidities such as obesity, diabetes, and HTA[15]. Regarding COVID-19 in patients with preexisting chronic liver disease (CLD), apart from the above-mentioned specific comorbidities, predictors such as CLD severity, related etiologies, and COVID-19 severity with breathlessness may lead to mortality[16]. However, the authors have suggested that the comprehensive relationship between these risk factors and the outcomes requires further studies. Regarding the COVID-19 pandemic, patients with fatty liver disorders (FLD) have a high risk of infection, and the incidence of FLD increases during containment periods[17]. These patients experience risk factors associated with the severity of infection, such as high BMI, metabolic comorbidities, and liver fibrosis, though FLD *per se* is an unconfirmed independent risk factor.

A high risk of liver defects has been reported in patients with MAFLD who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Monitoring of markers pertaining to heart, kidney, and liver function; muscle injury; and coagulation is required in patients with COVID-19. Due to the common polytherapy in COVID-19, such patients may experience drug-induced liver injury[18].

Silaghi-Dumitrescu *et al*[19] reported decreased insulin secretion, due to reduced insulin secretory granules from pancreatic beta cell, in patients with COVID-19. SARS-CoV-2 may alter the beta cells in the pancreas and trigger proinflammatory cytokine production. In AT, proinflammatory processes lead to persistent low-grade inflammation, which is involved in T2DM occurrence and IR pathogenesis. Hyperglycemia and IR have been reported in patients with COVID-19 without any history of diabetes. Apoptosis in SARS-CoV-2-induced thyroid lesions has also been reported [19]. Decreased blood plasma levels of antioxidant enzymes, such as glutathione peroxidase, glutathione, superoxide dismutase (SOD), and catalase, have been observed in patients with COVID-19, in addition to increased oxidative stress parameters, which increases the severity and mortality risks of the disease. Oxidative stress is influenced by inflammatory cytokine production, innate immune response activation, and infected cell death. Similarly, a reduction in glutathione rates due to factors such as dehydration, malnutrition, high urea levels, diarrhea, and increasing cyanate levels in patients with COVID-19 may trigger cataractogenesis.

Acute liver failure (ALF) and CLD are associated with diverse neurological alterations. Brain inflammation is involved in neurological disorders in patients with hepatic encephalopathy (HE). Gut microbiota dysbiosis, accompanied by impaired intestinal permeability, triggers bacterial translocation and endotoxemia, causing systemic inflammation such as neuroinflammation in brain tissue[20]. Furthermore, metabolites from the gut microbiota may alter the central nervous system, leading to neurological complications and worsening clinical manifestations. However, factors such as the etiology, comorbidities, disease severity, and external milieu may influence neuroinflammation and the gut microbiota. Hence, inhibiting neuroinflammation may be a promising strategy for HE management. Available therapeutic options are somewhat effective, and new approaches with clinical practice implications have been suggested[20].

The pathogenesis of osteopenia and osteoporosis in patients with NAFLD remains poorly understood. A high prevalence of NAFLD has been reported in patients with obesity, which may lead to sarcopenia, regardless of the patient's age. Authors have hypothesized the possible occurrence of osteopenia and osteoporosis in these patients because the metabolism, biological function, and skeletal muscle are closely linked to bone health. They have suggested further research pertaining to osteopenia, osteoporosis, and sarcopenia in patients with NAFLD[21].

Heart disease has been linked to abnormal iron levels, both low and overloaded[22]. Systemic iron metabolism is regulated by hepcidin itself induced by IL-6. Hepcidin is an acute-phase protein released by the liver in response to inflammation. During inflammation, the homeostasis of systemic iron is dysregulated, which may lead to low blood iron levels[22]. Thus, the underlying mechanisms of iron regulation and inflammatory processes are linked, and these processes occur in the cardiovascular system, particularly in heart diseases. Iron regulation in cardiomyocytes is well-understood; however, little information is available on 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 promising way to prevent and treat inflammatory processes that lead to cardiovascular disease disorders or complications.

Psoriasis has been linked to a high risk of NAFLD. Screening for NAFLD and its associated comorbidities is recommended for all patients with psoriasis. The authors have suggested conducting prospective controlled experiments to assess the effectiveness of biological treatments in preventing NAFLD progression in these patients[23].

NAFLD and alcohol-related liver disease (ALD) share disease pathophysiological, histological, and genetic characteristics. Alcohol consumption and metabolic dysfunction have also been reported as coexisting etiological factors in patients with hepatic steatosis[24]. In patients with fatty liver disease, the authors have suggested assessing both causality factors such as MetS and alcohol consumption, to provide a better prognosis and personalized medicine approach.

Cardiometabolic risk factors should be considered when categorizing patients with steatotic liver disease (SLD). Moreover, a mixed subtype, metabolic dysfunction-associated SLD, combined with high alcohol intake (MetALD), highlights patients with moderate or high alcohol intake who have been ignored. However, this new nomenclature does not precisely determine the contribution of metabolic dysfunction and alcohol intake to the development and evolution of SLD[25].

Fibrosis is defined as an increase in fibrous connective tissue and a decrease in parenchymal cells in organs or tissues, including the lungs, heart, liver, kidneys, and skin. Long-term fibrosis may trigger organ and tissue dysfunction and subsequent failure. The IL-1 family of cytokines is involved in the occurrence and progression of diverse fibrotic diseases. Consequently, their biology, association with diseases, and clinical applications have attracted interest worldwide[26]. Eleven cytokines and ten receptors have been identified in the IL-1 family[26]. IL-33, a cytokine with high profibrotic potency in the IL-1 family, is involved in the occurrence and progression of diverse fibrotic pathophysiologies. Hampering its signaling pathway decreases fibrosis levels in animal models. However, the clinical application of its specific neutralizing antibody or receptor ST2 inhibitor requires confirmation. Some researchers have questioned the possibility of directly applying IL-1Ra- and IL-37-related drugs as clinical treatments. Further studies should focus on the comprehensive signaling pathways, regulatory mechanisms, and therapeutic targets in fibrotic disease therapies. In terms of research on the IL-1 family, basic research (*i.e.*, drug development) is valuable. A thorough understanding of the roles and mechanisms of the IL-1 family members will enable the development of more effective drugs to prevent and treat fibrotic diseases[26].

Autoimmune liver diseases include different types of chronic disorders, such as autoimmune hepatitis, the primitive form of biliary cholangitis, and sclerosing cholangitis. Patients with liver cirrhosis and NAFLD may experience glucose disturbances, such as IR, and are at a high risk of developing diabetes. Despite the scarcity of evidence pertaining to glucose disturbances among patients with autoimmune liver disease, there is the potential of a greater risk of type 1 diabetes and T2DM[27]. Although the underlying mechanisms are unknown, some potential explanations include a genetic predisposition, concurrent NAFLD or cirrhosis, and steroid therapy leading to impaired glucose homeostasis. Hence, improving the awareness and surveillance of diabetes in patients with autoimmune liver disorders may be of interest. The existing guidelines for diabetes management may serve patients experiencing advanced hepatic cirrhosis, in which HbA1c may be an unreliable marker and insulin therapy is *a fortiori* recommended. Furthermore, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been suggested as useful treatments for refractory ascites[27].

The cross-linkage between metabolic abnormalities and the innate immune system during the occurrence and evolution of NAFLD has been well documented[28]. A better understanding of these bidirectional links will significantly improve patient management. Furthermore, lipid metabolic abnormalities and the innate immune system connect NAFLD to atherosclerosis, which is of great clinical interest[28].

Liver disease comorbidities, risk factors, and the related pathobiology and pathophysiology are summarized (Table 1).

COMORBIDITY IMPACT ON IL-MEDIATED THERAPY IN LIVER DISEASES

Comorbid pathologies, including, obesity, T2DM, and CVD, can trigger hepatic disorders, which makes managing liver diseases with conventional medicines challenging. In addition, unsafe prescriptions, polytherapy, misuse or overuse of drugs, and adverse drug reactions (ADRs) may further complicate management[29]. The production of harmful cytokines, including IL-1β, tumor necrosis factors (TNF-α), nuclear factor (NF)-κB, activator protein (AP-1), macrophage inflammatory protein (MIP), and toll-like receptor (TLR4), has been assessed for clinical significance owing to a complicated liver state and evidence-based recommendations. Liver fibrosis mediators, such as the transforming growth factors (TGF-β), matrix metalloproteinases (MMPs), and extracellular matrix (ECM), have been identified as interesting targets[29]. Recent investigations have shown multiple benefits of polyphenol-based therapy, as these molecules have protective effects on cellular components such as the membrane, cytoplasm, and genetic materials. As there is no effective treatment for fibrosis, daily consumption of citrus polyphenols can be an effective alternative. Pharmacological data have shown that citrus fruits are extremely effective and well-tolerated. Hence, citrus-derived polyphenols are recommended for the prevention of multiple chronic diseases. Numerous potent and highly effective components have been isolated,

Table 1 Liver diseases and related comorbidity, risk factors and pathophysiological mechanisms

Liver diseases	Comorbidity/condition	Risk factors and pathophysiology
NAFLD	CKD	NAFLD (a liver manifestation of MetS) shares with CKD diverse cardiometabolic risk factors such as: hyperuricemia, dyslipidemia, abdominal-obesity, pro-inflammatory state, hypoadiponectin, and a prothrombotic-hypofibrinolytic event[6]
	AT (dysfunction), IR	AT dysfunction is an important factor involved in the occurrence of NAFLD and IR[9]
	NASH, MetS, CVD, T2DM, CKD, HCC	Morbidity and mortality in NASH patients the mostly exacerbated by the occurrence of CVD, T2DM or CKD. HCC can poorly lead to NASH progression in the affected individuals. MetS and CVD are mainly responsible for NAFLD mortality; whilst NAFLD comorbidity with CKD and diabete increases CVD mortality[10]
	Osteoporosis	NAFLD prevalence can reach 85% in patients with obesity. NAFLD and osteoporosis reported clinically and pathologically associated, mainly in elderly and senile patients[21]
	Psoriasis	Psoriasis patients experienced a high risk of NAFLD, as well as an increase in the levels of adipokines and hepatokines[23]
MAFLD	CKD	MAFLD reported significantly associated to CKD prevalence and incidence[7]
	SARS-CoV-2 (infection)	COVID-19 involved in glucose homeostasis alteration, inflammatory cytokines storm, and oxidative stress increase, which may worsen MAFLD state[18]
ALF/CLD	HE	ALF and CLD may trigger HE (a neurological alteration). Pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) release into brain, following microglial cells activation, characterizes neuroinflammation. That neuroinflammation may impair neurotransmission, which induces the both cognitive- and motor- dysfunction[20]

NAFLD: Nonalcoholic fatty liver disease; CKD: Chronic kidney disease; MetS: Metabolic syndrome; AT: Adipose tissue; IR: Insulin resistance; CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus; HCC: Hepatocellular carcinoma; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; ALF: Acute liver failure; CLD: Chronic liver disease; HE: Hepatic encephalopathy; TNF: Tumor necrosis factors; IL: Interleukin.

including caffeic acid, naringenin, and limonin. Large-scale clinical trials are required to determine the accurate therapeutic doses of these components to design next-generation drugs. Large-scale trials can elucidate powerful drug molecules in citrus fruits[29].

As for cytokines, since long-lasting anti-inflammatory responses and a persistent proinflammatory course may not benefit infected patients, their implications for the host's antiviral defense have been questioned[12]. Consequently, further research is required to accurately understand their mechanisms of action in targeting viral infections. Hence, the challenge is to develop cytokines into effective antiviral therapies, which requires rigorous research to ensure safe, long-lasting, and effective antiviral formulations.

Regarding COVID-19, the genetic polymorphisms rs12979860 and rs1298275 of IL-28B have been frequently described as unfavorable for pathologies such as hepatitis C and HCC. The great genetic variability of human leukocyte antigens (HLA) is a crucial factor that is relevant to the late immune response, owing to its ability to recognize antigens, and the HLA-B*46:01 single nucleotide polymorphism has been linked to COVID-19 susceptibility. For IL-6, rs1554606 has been strongly correlated with COVID-19 clinical progression, whereas rs2069837 has been identified as being capable of protecting the host against this infection[13].

A 'cytokine wave' may occur in COVID-19, leading to a molecular pathophysiological state with possible multiorgan failure[14,19]. Potential liver injury in patients with COVID-19 has been reported, as demonstrated by hepatic laboratory parameters, such as the levels of ALT, AST, bilirubin, and albumin[14]. The liver is implicated in protein synthesis and drug metabolism through cytochrome P450 (CYP); consequently, minor alterations in liver function may significantly affect the hepatic clearance of xenobiotics or chemical exposure of an organism. High cytokine levels are common in patients with COVID-19. Similarly, patients with non-SARS-CoV-2 infection experience suppression of CYP enzymes in an infection-related cytokine increase and an inflammatory course[13]. In addition to interventional COVID-19 drug uptake, patients may also be receiving a therapeutic regimen for comorbidities. Observational studies have shown that patients with HTA, hyperglycemia, or obesity are more susceptible to COVID-19. This raises drug- and disease-interaction issues, since interventional drugs (*e.g.*, remdesivir and dexamethasone) and agents against comorbidities may be affected by compromised CYP-mediated liver metabolism. Therefore, caregivers of patients with COVID-19 should pay attention to CYP-driven drug metabolism interactions, either by adjusting the drug dose or discontinuation, as appropriate[14].

Alternative medicine (traditional therapy) may enable fewer ADRs or interactions and cost-saving options[29]. Seasonal fruits, such as citrus, are known for their medicinal value and are widespread worldwide. This fruit has diverse biological activities owing to its chemical components, such as polyphenols, flavonols, carbohydrates, amino acids, and oils. Polyphenol-based molecules are highly effective against the production of inflammatory cytokines and profibrogenic factors. These molecules may prevent free radical formation and oxidative stress. Moreover, polyphenols trigger the induction of useful functional proteins and mitochondrial biogenesis *via* protective genes, including AMPK, SOD, catalase, and heme oxygenase.

Psoriasis and NAFLD share diverse pathophysiological events such as systemic inflammation and IR. Hence, preventing or altering the systemic inflammatory process may be useful for reducing or improving NAFLD progression [30].

While the Western diet may affect gut permeability and its microbiota components and function, leading to the selection of pathobionts, the Mediterranean diet reinforces health-beneficial microbiota, positively affecting lipid and glucose metabolism and the hepatic inflammatory process[31]. The use of antibiotics and probiotics improves NAFLD characteristics, with mitigated results. Furthermore, NAFLD-associated comorbidity medications may modulate the gut microbiota. Medicines used to treat T2DM, such as metformin, glucagon-like peptide-1 agonists, and SGLT inhibitors, have several benefits, including effective regulation of glucose homeostasis, reduction of liver fat content and inflammation, and changes in intestinal microbiota components towards a healthy profile. Bariatric surgery can cause changes in the gut microbiota, which affects the gastrointestinal anatomy and improves the histological state of NAFLD. Further research pertaining to fecal microbial transplantation (FMT) and next-generation probiotics is being conducted to develop new therapeutic tools for NAFLD[31].

Lactobacillus acidophilus (*L. acidophilus*) KLDS1. 0901 contributes to high-fat diet (HFD) -induced NAFLD therapy by improving liver features and modulating microbiota components. Hence, this bacterium may be a candidate for the optimization of NAFLD treatment[32]. In an animal model study, *L. acidophilus* KLDS1. 0901 uptake reduced IL-6, IL-1β, and TNF-α levels with an increase in the IL-10 concentration. This administration can improve the gut barrier function by upregulating the mRNA expression levels of some molecules, such as occludin, claudin-1, ZO-1, and Muc-2, while decreasing the levels of lipopolysaccharide and D-lactic acid. Furthermore, the uptake of *L. acidophilus* KLDS1. 0901 modulates the intestinal microbiota towards a normal profile. Therefore, *L. acidophilus* KLDS1. 0901 may be a useful candidate for improving NAFLD[32].

Pomegranate (*Punica granatum*) is a functional food with diverse beneficial properties and health effects. Jafarirad *et al* [33] reported that pomegranate extract significantly decreases the levels of markers such as ALT, AST, gamma-glutamyl transferase, fetuin-A, fibroblast growth factor 21, and IL-6 in patients with NAFLD compared to the placebo group. Pomegranate may be a useful supplemental therapy since its extract has an improved effect on most NAFLD-related laboratory parameters[33]. While this medicinal extract can lead to an increase in total antioxidant capacity, it does not show any effect on alkaline phosphatase. Furthermore, that study showed that a daily intake of 450 mg of pomegranate extract (*i.e.*, two tablets standardized based on 40% ellagic acid) for 12 weeks reduced the levels of hepatic enzymes, hepatokines, and IL-6, thus increasing the total antioxidant power[33].

SGLT2 inhibitors play a beneficial role in preventing hospitalization for decompensated cardiac failure and in protecting the kidney, which limits the deterioration of glomerular filtration in patients with or without diabetes mellitus [34]. These medicines prevent ASCVD and death caused by cardiovascular events in patients with concomitant diabetes and cardiovascular disorders. Patients with T2DM may have a high associated comorbidity burden such as HTA, dyslipidemia, hyperuricemia, obesity, NAFLD, polycystic ovary syndrome (PCOS), vascular aging, breathing disorders, and osteoporosis. Integrated and pluralistic approaches should be applied for the management of these patients. The authors suggested further studies to corroborate the effectiveness of SGLT2 inhibitors in non-diabetic disorders such as hyperlipidemia, PCOS, or vascular aging[34].

Hepatic inflammation and fibrosis are triggered by the activation of liver-resident macrophages (or Kupffer cells). Because of macrophage plasticity, these cells may be polarized into various phenotypes by different microenvironmental stimuli[35]. The polarization of macrophages into phenotypes such as M1 (with proinflammatory properties) or M2 (with anti-inflammatory effects) is regulated by complex cell-signaling pathways such us the phosphoinositide 3-kinase (PI3K)/Akt pathway. Inhibiting M1-type or promoting M2-type polarization may be an effective therapy against CLD, including ALD, NAFLD, and hepatic fibrosis. This cell-signaling pathway may act as a potential modulator of macrophage-related events, such as survival, migration, proliferation, and responses to metabolic and inflammatory signals. The anti-inflammatory cytokine expression induced by PI3K/Akt pathway activation promotes an M2-like phenotype, which facilitates tissue repair and inflammation resolution. Conversely, the inhibition of PI3K/Akt signaling can increase the M1-like phenotype, which increases liver impairment. Plant chemicals may be used to effectively treat CLD in future liver disease therapies by targeting the PI3K/Akt pathway to regulate the polarization of macrophages and their activity[35].

Patients with NASH have notable differences in terms of associated comorbidities, severity, and the level of control achieved by the different drugs. These comorbidities, in addition to their management, constitute an important source of heterogeneity between trial participants, which inevitably affects the evaluation of trial outcomes, adverse events, and patient compliance, as well as the real-world applicability of the results[36]. Moreover, these participants may also experience changes in the status of these comorbidities over the course of the trial, which can last years. Hence, to manage the comorbidities, a guidance that defines acceptable limits has been proposed by the Liver Forum regarding the management of comorbidities in NASH therapeutic trials. This guidance is intended to be compatible not only with the specifics of NASH, which is a multisystemic disease, but also with trial concerns, including its feasibility and integrity. Updates should be provided as concepts, treatments, and standards of care evolve[36].

Characteristics of NAFLD may overlap with those of MetS; when combined with the heterogeneity of disease mechanisms, this overlap may complicate the diagnosis and prognosis of this liver disorder and hinder research progress for biomarkers and drug discovery. Pirola and Sookoian[37] explored the heterogeneous clinical pattern of NAFLD using cluster analysis of molecular markers that serve as an approximation for the stratification of the disease into molecular subtypes. The authors reported unique biological pathways pertaining to each clinical subtype/group, including NAFLD and obesity, NAFLD and HTA, NAFLD and dyslipidemia, and NAFLD and T2DM. Therefore, a better understanding of the disease from a biological perspective can improve the management of patients with NAFLD, which requires dissecting the molecular subphenotypes responsible for disease progression[37].

The increasing socioeconomic burden of ALD has been reported worldwide; however, its frequency is underrated, and patients with ALD are rarely diagnosed at 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. The ALD spectrum ranges from steatosis, fibrosis, and cirrhosis to HCC, with chronic alcohol consumption of > 20 g/day for females and > 30 g/day for males. ALD is a clinical syndrome of progressive icterus that occurs in patients who exceed the normal daily alcohol intake. These patients may or may not present with ascites or HE. In severe AH, prednisolone is indicated as the first-line therapy, although complications may occur[38]. If prednisolone treatment fails, early-stage liver transplantation (LT) may be a useful option for selected patients. Abstinence is the cornerstone of long-term care, although relapse commonly occurs. Emerging treatment options focus on targeted approaches, such as preventing liver inflammation, decreasing oxidative stress, improving gut dysbiosis, and increasing hepatic regeneration. The promotion of precision medicine through multiomics analysis and consideration of sex is justified to overcome the challenges and obstacles in conducting successful clinical trials of patients with ALD[38].

Patients may experience life-threatening clinical states such as ALF and acute-on-chronic liver failure (ACLF). ALF is characterized by rapid liver dysfunction, coagulopathy, and HE in patients without CLD, while ACLF occurs in those with prior CLD[39]. These deadly diseases may drive diverse organ failures and early mortality. The cytokine IL-22 is produced by immune cells and specifically targets epithelial cells, such as hepatocytes. Preclinical models and clinical trials of AH have reported that IL-22 protects against organ damage and reduces bacterial infection. The hepatoprotective effect and immunomodulating capacity of IL-22 have been observed in preclinical models of ALF and ACLF, in addition to positive results provided by clinical trials for other liver and inflammatory diseases, especially AH, which allows the prediction of the efficacy of IL-22[39].

Although LT outcomes have improved in recent years, long-term morbidity and mortality remain[40]. Graft function and comorbidities, including MetS complications, are not responsible for most late deaths. However, recent issues appear to be linked to *de novo* neoplasms in LT recipients. However, a long-term strategy for LT recipient management through drug toxicity reduction, high-risk patient identification, and multidisciplinary team collaboration may further increase the post-LT survival rate[40].

Liver injury may be triggered by inflammatory and innate immune responses leading to Kupffer cell activation. The liver-specific cell activation allows the release of multiple cytokines, including IL-6, IL-1β, and TNF-α[41]. A liver-related co-mitogen, augmenter of liver regeneration (ALR), has been reported to have antioxidative and anti-apoptotic properties, in addition to a reducing effect on NAFLD and cholestasis. Moreover, patients with NAFLD or cholestasis experience decreased ALR expression, although the underlying mechanisms of its regulation (under these conditions) are unclear. Furthermore, IL-1β therapy reduces ALR promoter activity, mRNA, and protein expression. IL-1β can induce the early growth response protein-1 (Egr-1), an ALR inducer, without activating the expression of ALR. That IL-1β-related property may be explained by a defect in the binding of Egr-1 to the ALR promoter[41]. Moreover, IL-1β reduces the expression and nuclear localization of hepatocyte nuclear factor 4α (HNF4α), another factor that induces ALR transcription. Importantly, c-Jun, a transcription factor and potential regulator of ALR and HNF4α, has shown an increased nuclear phosphorylation level following IL-1β therapy. However, ALR or HNF4α expression is unchanged by c-Jun. IL-1β regulates anti-apoptotic and antioxidative ALR *via* reduced Egr-1 promoter binding and decreased HNF4α expression independent of c-Jun activation[41]. Therefore, the low ALR levels in the tissues of patients with NAFLD and cholestatic liver injury may be due to IL-1β, contributing to disease progression. As for IL-1 inhibitors, clinical experiments are rare and do not allow the elucidation of their beneficial role in NAFLD therapy, even if preclinical investigations are promising[42]. Moreover, most evidence pertaining to treatment with IL-1 family members comes from preclinical experiments. Owing to the lack of clinical data and access difficulties, achieving beneficial results from IL-1 family members in clinical practice requires further research[43].

Hepatocellular death is a fundamental biological process that regulates the progression of liver disease *via* distinct mechanisms. The involvement of the IL-1 family in liver cell apoptosis has been widely reported[44]. Promoting new and innovative management approaches pertaining to liver diseases through close collaboration between fundamental and clinical scientists should provide a comprehensive understanding of the complex processes involved in the contribution of the IL-1 family of cytokines to hepatocellular apoptosis[44].

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

CONCLUSION

NAFLD and CKD have common cardiometabolic risk factors, including MetS, IR, T2DM, uricemia, dyslipidemia, abdominal obesity, proinflammatory milieu, hypoadiponectin, and a prothrombotic-hypofibrinolytic state. MAFLD is significantly associated with the risk of CKD. Patients with T2DM may have several comorbidities or conditions, including HTA, dyslipidemia, hyperuricemia, obesity, NAFLD, PCOS, vascular aging, breathing disorders, and osteoporosis. Therefore, an integrated, pluralistic approach is a better option for managing these patients. Comorbidities and their management, as an important source of heterogeneity between trial participants, can impact the trial evaluation regarding outcomes, adverse events, patient compliance, and the applicability of trial results in the real-world.

The comorbid pathologies may be responsible for liver disorders, which makes treating hepatic diseases with conventional drugs challenging. Moreover, unsafe prescriptions, polytherapy, inadequate use of drugs, and ADRs may complicate management. The production of harmful cytokines, such as IL-1β, TNF-α, NF-κB, AP1, MIP, and TLR4, have been assessed for clinical significance, owing to the complicated liver state.

The clinical subtypes and groups have unique biological pathways, including NAFLD and obesity, NAFLD and HTA, NAFLD and dyslipidemia, and NAFLD and T2DM.

IL-22 has been reported to have hepatoprotective and immune-modulating effects on both ALF and ACLF, in addition to its positive effects in clinical trials on other liver and inflammatory diseases, such as AH. Conducting IL-mediated monotherapy and synergistic treatment experiments may provide scientific and new drug development insights. In addition, judicious exploitation of newly available data pertaining to comorbidities and a multidisciplinary approach should efficiently address short-term liver disease management and prevent long-term complications.

FOOTNOTES

Author contributions: Bouare N designed, drafting and contributed to reviewing the manuscript; Delwaide J contributed by drafting and reviewing the manuscript; All authors reviewed, read and approved the final version of the manuscript.

Conflict-of-interest statement: Any conflict of interest to disclose.

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S-Editor: Gao CC
L-Editor: A
P-Editor: Ma XP

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