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ANALYSIS OF PRINCIPLES FOR IMPROVING OPTIMAL TREATMENT MEASURES FOR LIVER AND BILE DUCT DISEASES

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Abstract. A chronic autoimmune liver disease called primary biliary cholangitis (PBC) is characterized by the destruction of the bile duct, which results in fibrosis and cholestasis. There are still gaps in patient-centered care, therapy response evaluation, and diagnostic standardization despite therapeutic breakthroughs. The goal of this study was to optimize PBC management by using consensus-driven quality measures. 92 clinicians took part in two rounds of questionnaires that included patient-reported outcomes (PROs), follow-up criteria, therapeutic approaches, and diagnostic methods using the Delphi methodology. The RAND/UCLA technique was used to analyze appropriateness evaluations in order to get a consensus on important quality metrics.The suitability of non-invasive diagnostic techniques such abdominal ultrasound and Vibration-Controlled Transient Elastography (VCTE) for staging and tracking fibrosis in chronic cholestasis was widely agreed upon. Patients with compensated cirrhosis (Child-Pugh A) and inadequate response to UDCA were investigated for various treatment options; early initiation was considered appropriate in cases of UDCA intolerance or partial response. Consensus on genetic tests and liver biopsies varied, especially for patients lacking biochemical cholestasis, indicating areas that require more investigation. This study provides detailed suggestions on diagnostic procedures, therapy benchmarks, and follow-up requirements in order to establish practical quality measurements for PBC care. By filling in gaps in patient categorization, follow-up procedures, and tactics, these actions go above and beyond recommendations. Cost-effectiveness, non-invasive tool accessibility, and implementation issues including physician training and resource availability should all be covered in future studies.

Keywords. Primary biliary cholangitis (PBC), obeticholic acid (OCA), non-invasive diagnostic techniques, Delphi consensus process, quality metrics in PBC treatment.

Introduction. Globally, chronic liver disorders are becoming more common, and each year, about 1.7 million fatalities are documented. Chronic liver illnesses have a complex aetiology, and research in the literature suggests that these causative factors differ depending on the region. Chronic viral infections (such as hepatitis B and C), excessive alcohol use, non-alcoholic fatty liver disease (NAFLD), inherited diseases (such as Wilson's disease, biliary fibrosis, and primary sclerosing cholangitis (PSC)), drug side effects, hazardous chemicals, and idiopathic or cryptogenic causes are the main causes. The events linked to the pathophysiology and fibrogenic development of chronic liver injury seem to share intracellular pathways regardless of the aetiology. The liver's wound-healing reaction to recurrent insult is what causes hepatic fibrosis. As a result, hepatocytes are replaced with an abundance of extracellular matrix (ECM), which eventually causes an accumulation of excess fibrotic scar tissue, and the balance between parenchymal cell regeneration and the wound healing response is shifted towards the wound

healing response with impaired regenerative pathways over time [1-5]. Chronic liver illnesses lead to cirrhosis, when fibrous tissue replaces a large portion of the hepatic parenchymal tissue, changing the liver's architecture and causing septae and nodule formation. This causes collateral development and changes in blood flow, which eventually lead to cirrhosis and liver failure. There are no established medical therapies for cirrhosis, and the ultimate therapy for this condition is liver transplantation, which is limited by the lack of donor livers and carries the risk of post-transplantation complications. Thus, there remains a major need to identify potentially modifiable factors that exacerbate liver injury and fibrosis, and to develop therapies that can prevent or slow liver scarring. Liver injuries are categorized into three major groups: cell-indiscriminate, cholestasis and hepatocyte-associated injuries. Mechanical trauma, ischemia and liver resection lead to cell-indiscriminate, whilst either mechanical or autoimmune bile duct injuries cause cholestasis. The major types of hepatocyte-associated injuries are either direct injuries (alcohol, drugs and hepatotropic infectious viruses, such as hepatitis B and C) or immune-mediated. The wound repair response occurs when liver tissue deposits extracellular matrix (ECM) in response to ongoing injury, irrespective of the original source. Furthermore, ECM production is thought to be an attempt by liver tissue to encapsulate the injured area in order to localize the harm [6-11]. Even though it is a crucial step in the healing of wounds, when it is dysregulated, the problem develops into "liver fibrosis," which is an ineffective attempt to restructure the liver tissue. Therefore, the excessive buildup of extracellular matrix (ECM) in the liver parenchyma that replaces functional hepatic tissue is the primary characteristic of liver fibrosis. A diagnostic algorithm, the updated nutritional therapy flowchart, and refracted ascites—all of which are crucial for cirrhosis patients—are the first topics covered. The most recent treatments for non-viral cirrhosis, such as alcoholic steatohepatitis/non-alcoholic steatohepatitis (ASH/NASH) and autoimmune-related cirrhosis, are also discussed, along with the revised antiviral therapy for hepatitis B and C liver cirrhosis. The most recent research on the diagnosis and management of complications associated with liver cirrhosis, such as gastrointestinal bleeding, ascites, hepatorenal syndrome and acute kidney injury, hepatic encephalopathy, portal thrombus, sarcopenia, muscle cramp, thrombocytopenia, pruritus, hepatopulmonary syndrome, portopulmonary hypertension, and vitamin D deficiency, including BQ, CQ, and FRQ [12-17]. Lastly, prognosis prediction and liver transplantation are covered in this guideline, with particular attention paid to a number of recent discoveries. The identical text is simultaneously published in the official English journals of JSGE and JSH because this revision is a collaborative guideline by both societies. This guideline supports clinical practice by outlining the components of medical treatment that can be suggested and suggested. It is based on evidence up to 2019 about the management of liver cirrhosis. Patients with cirrhosis have a wide range of disease states, and certain medical treatments are not covered by insurance. When implementing this recommendation, please keep these considerations in mind and take the necessary precautions, such as refraining from using it for purposes other than medical treatment [18-23].

The main purpose of the presented manuscript is to provide a brief analysis of the principles of improving optimal treatment measures for liver and biliary tract diseases based on the results of authoritative scientific works.

Biliary diseases. Cholestasis and increasing biliary fibrosis, which can result in end-stage liver failure, are the hallmarks of a set of chronic liver illnesses known as biliary diseases or cholangiopathies. These illnesses have many different causes. Immune diseases, primary biliary cholangitis/primary biliary cirrhosis (PBC), and PSC are two prevalent cholangiopathies. Cholangiopathies can also be caused by infectious agents of bacterial, viral, or fungal origin, vascular or ischemic reasons (such post-liver transplantation), hepatic artery stenosis,

medications or toxins, and genetic abnormalities (like cystic fibrosis). Idiopathic ductopenia and biliary atresia are examples of idiopathic cholangiopathies. Small bile ducts are the main target of many cholangiopathies, such as PBC and drug-induced cholangiopathies. On the other hand, conditions such as PSC and cholangiocarcinoma impact both the big bile channels inside and outside the liver. Bile builds up in the liver after bile flow is compromised, initially harming the biliary epithelium and ultimately the liver parenchyma. Peri-portal inflammations that result in liver fibrosis or cirrhosis are common to most cholangiopathies. The majority of cholangiopathies constitute a key indication for liver transplantation because of their progressive nature, which results in significant morbidity and mortality in patients [8-18].

The pathogenesis of biliary fibrosis and cholestasis. A reduction in bile flow brought on by either hepatocyte secretion impairment or bile flow obstruction is known as cholestasis. Both intrahepatic and extrahepatic factors can cause bile flow obstruction. Extrahepatic bile duct obstruction is referred to as an extrahepatic cause of cholestasis, whereas intrahepatic bile duct obstruction and changes in bile secretion by hepatocytes are regarded as intrahepatic causes. Increased bile buildup inside hepatocytes results in initial injury to the biliary epithelium and ultimately the liver parenchyma once bile flow is compromised. Small bile ducts are the main target of many cholangiopathies, such as PBC and drug-induced cholangiopathies. Both intrahepatic and extrahepatic big bile ducts are impacted by conditions like PSC and cholangiocarcinoma. Two primary mechanisms are in charge of both biliary homeostasis and cell healing in chronic cholestatic liver injury. The first is the growth of existing bile ducts due to the proliferation of cholangiocytes from both small and big damaged bile ducts [5-13]. The second route involves the activation of oval cells or hepatic progenitor cells (HPCs), which develop into cholangiocytes and create new bile ducts—a process known as a "ductular reaction." These newly formed ductules will eventually form a tubular network that restores the ductal mass in an attempt to prevent further liver injury and the leakage of bile acids into the liver parenchyma. In order to sustain newly formed tubules, a fibro-vascular stromal area is developed as a result of extensive cross-talk between hepatocytes, HSCs, LSECs and KCs. On the other hand, ductular reaction is accompanied by continuous inflammatory signals resulting from key signalling molecules, such as TGF-β1, TNF-α and vascular endothelial growth factor, which then lead to liver fibrosis and later cirrhosis [15-20].

Current cholangiopathy treatment options. The most prevalent cholangiopathies in humans are thought to be PBC and PSC. Both disorders result in end-stage liver failure, which is a sign that a liver transplant is necessary. Following the therapeutic usage of ursodeoxycholic acid (UDCA) in PBC patients, there has been a decline in the number of liver transplants for PBC in the US and Europe. It has not been shown to be an effective treatment for any other cholangiopathies, while being the sole FDA-approved medicinal treatment for PBC. There is currently no evidence that the number of PSC patients designated for liver transplantation has decreased. PSC is the second most frequent cholangiopathy for which there is no specific medicinal treatment. This suggests that there is no medication that effectively stops PSC patients from developing cirrhosis. Furthermore, PSC recurrence following liver transplantation highlights the urgent need for a successful medical treatment for this illness. Regardless of the underlying cause of the condition, the development of antifibrotic medicines shows promise in the treatment of liver fibrosis, including biliary disorders [3-12]. By preventing the activation of myofibroblastic cell populations, they can either stimulate the breakdown of extracellular matrix (ECM) or prevent the creation of excess ECM. The primary obstacle, however, is the lack of an efficient antifibrotic treatment with few or no adverse effects. Therefore, for patients with biliary fibrosis, liver transplantation has unavoidably become their only option. The current scenario is made worse by a rise in chronic liver disease, a shortage of donor organs, post-transplant

problems, and the high expense of liver transplantation. Therefore, the development and formulation of targeted, efficient, safe, and affordable medical treatments is imperative. The local renin-angiotensin system (RAS) is an intriguing target for the development of antifibrotic treatments. The RAS is essential for blood pressure control, salt and water homeostasis, and post-injury tissue remodeling in normal physiology. The inevitable production of off-target effects, which are frequently unwanted, is a significant drawback of systemic therapy. Therefore, systemic administration of rACE2 has a number of drawbacks. This involves daily ACE2 injections, which are a costly and intrusive treatment in a clinical environment. Off-target effects, such as an impact on blood pressure, are quite likely to result from elevated circulating ACE2. Increasing tissue- or organ-specific ACE2 levels would be the best way to get around this difficulty. Therefore, organ-specific elevated ACE2 activity would reduce undesirable off-target effects while also producing long-term organ-specific benefits [14-22].

Overexpression of ACE2 in the liver. Transgenes can be safely and effectively inserted into particular tissues or organs using viral vectors.Adeno-associated viral (AAV) vectors are frequently employed in Phase I–II clinical trials and seem to be the safest and most effective of the viral vectors that have been used to date to improve the delivery of genes.Replicative defectiveness, non-pathogenicity, minimal immunogenicity, and broad tissue tropism in both human and animal models are just a few of the many benefits that the AAV vector offers over other potential viral vectors. It has been demonstrated to be effective in delivering a transgene. Because the AAV system can sustain long-term gene and protein expression after a single vector injection, it has gained popularity as a gene delivery technique. The FDA's 2017 approval of a ground-breaking gene therapy regimen utilizing an AAV vector for a rare kind of infant blindness is noteworthy because it was the first such treatment approved for an inherited disease in the US. Additionally, the European Commission authorized the use of the AAV vector in gene therapy in 2012 to treat patients with lipoprotein lipase deficiency (LPLD) [5-13]. However, UniQure, the firm that created the AAV vector to treat LPLD, did not renew its EU license in 2017 because LPL insufficiency is a very uncommon genetic illness in humans and the treatment is costly. Accordingly, our team has created a safe and efficient therapeutic strategy utilizing a pseudotyped AAV vector that delivers murine ACE2 (AAV2/8-mACE2) using the AAV2 genome and liver-specific AAV8 capsid (AAV2/8). This demonstrated that liver ACE2 expression can be sustainedly elevated for up to six months following a single intraperitoneal injection of rAAV2/8-mACE2. Three short-term mouse models of liver disease—liver disease caused by BDL (2-week model), CCl4 (8-week model), and a diet deficient in methionine and choline (8-week model)—were given the treatment. These models represented alcoholic liver fibrosis, cholestatic biliary fibrosis, and nonalcoholic fatty liver disease, respectively [17-22].

Discussion. Hepatic fibrosis, cirrhosis, and/or hepatocellular cancer are the inevitable outcomes of chronic liver disorders, which are now a leading cause of disease and mortality globally. Cholangiopathies, often known as cholestatic liver disorders, are a broad category of illnesses that mostly affect the biliary system. These include acquired conditions like primary sclerosing cholangitis and primary biliary cirrhosis, congenital conditions like biliary atresia and cystic fibrosis, and conditions resulting from secondary damage to the biliary tree caused by blockage, cholangitis, or ischaemia. These disorders are linked to a particular pattern of long-term liver damage that is focused on bile duct destruction, which causes peribiliary fibrosis and, eventually, biliary cirrhosis and liver failure. These conditions continue to be among the most significant indications for liver transplantation because there is no proven medicinal treatment for the majority of them. The development of novel treatments that can stop the progression of chronic biliary damage and fibrosis is therefore crucial [2-9]. The mechanism of liver fibrosis and how it develops into cirrhosis are briefly covered in this mini-review. We focus particularly

on biliary fibrosis and available treatments, such as the over-expression of angiotensin converting enzyme-2 (ACE2) in the affected liver as a novel prospective treatment. The pathogenesis of chronic liver fibrosis is the main topic of this mini-review, with biliary fibrosis receiving particular attention. Additionally, we made an effort to address the benefits and drawbacks of existing commercially accessible treatments for biliary fibrosis as well as additional possible treatments that are still in the preclinical stage of development. Specifically, research from the author's lab reported in this review shows that in animal models of biliary illness, liver-specific over-expression of angiotensin converting enzyme-2 (ACE2) of the alternative renin angiotensin system significantly lowers biliary fibrosis. This implies that patients with persistent biliary fibrosis may benefit from ACE2 gene therapy. The Japanese Society of Gastroenterology (JSGE) released the first edition of the clinical practice guidelines for liver cirrhosis in 2010 and the second edition in 2015. 2020 saw the release of the updated third edition. The Japan Society of Hepatology (JSH) and the JSGE have adopted this version as a joint guideline [11-17]. Future research questions (FRQs) are new clinically significant items, while background questions (BQs) are new items for fundamental clinical knowledge in addition to the clinical questions (CQs). Over the five years since the second edition, additional research on the clinical management of liver cirrhosis has been published. By consulting the most recent international criteria, we made the decision to align this modification as closely as feasible with international standards. Additionally, there has been significant advancement in the development of new agents for a variety of issues. We are presenting data based on evidence for clinical practice in Japan in contrast to the most recent international guidelines, such as those published by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL). By consulting international criteria, the nutrition therapy flowchart was evaluated to be helpful for everyday medical care. We also discuss a number of clinically significant topics that were not included in the previous editions but have recently gained attention. The therapy of liver cirrhosis and its consequences in clinical practice are discussed in this condensed version [18-23].

Conclusions. Although UDCA is the primary treatment for PBC in clinical practice, statistics show that between 35% and 40% of PBC patients do not respond optimally to UDCA. However, research on PSC patients revealed that while ordinary dosages of UDCA are ineffective, higher doses cause substantial side consequences. PSC, along with other cholangiopathies, is a significant biliary illness. Therefore, the absence of an effective medication for biliary illnesses is frequently linked to the condition's progression to biliary cirrhosis and carries the risk of evolving into cholangiocarcinoma or HCC. For individuals with chronic cholangiopathies, such as end-stage PSC and PBC, liver transplantation is therefore thought to be the only course of treatment.

However, there is a significant unmet need to discover effective treatments for these illnesses due to the lack of donor livers. By delivering ACE2 utilizing human liver-specific new vectors with high transduction efficiency, ACE2 gene therapy is a possible treatment for human biliary fibrosis. As a result, choosing an AAV vector with improved transduction efficiency that is unique to human hepatocytes is crucial. According to recent research, new AAV vectors that were discovered using AAV DNA re-shuffling—such as AAV-LK03, AAV3B, and AAVrh10—transduce human primary hepatocytes more effectively. The development of therapeutic gene therapy applications for human biliary fibrosis will result from innovative gene therapy research methods that use human liver-specific AAV vectors, as the FDA and EU have now approved human gene therapy.

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