

## **Editorial: THE TREATMENT OF LIVER DISEASES IN 2020-2030**

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The liver is a multifunctional organ that is essential for life. Several diseases can damage the liver and ultimately lead to cirrhosis, liver failure and hepatocellular carcinoma, if left untreated. Liver diseases account for approximately 2 million deaths per year worldwide, which probably is an underestimation. In addition, the economic cost is high and quality of life is impaired in patients with chronic liver disease. Therefore, timely diagnosis and effective interventions to prevent and reverse advanced liver disease are needed to improve the outcome of liver patients. In this special issue of COPHAR, we provide an up-to-date overview on the treatment of liver diseases, with a focus on current and future pharmacological approaches. This information is bundled in 11 expert review articles.

Alcohol is the most prevalent cause of cirrhosis and alcohol-related liver disease is the most prevalent indication for liver transplantation. Achieving and maintaining abstinence is a key-determinant for survival in patients with alcohol-related liver disease, but is challenging in patients with an alcohol use disorder (AUD). In addition to psychiatric support, pharmacological options for the treatment of AUD exist, but inexperience with prescribing these drugs and potential safety concerns related to the liver hamper their use. Maja Thiele and colleagues discuss the current pharmacological treatment options for **AUD** in patients with liver disease and provide a practical framework.

**Severe alcoholic hepatitis** is a life-threatening clinical syndrome whereby patients with alcohol-related liver disease suddenly develop jaundice and liver failure. These patients have a high short-term mortality of 20-50%. Corticosteroids are the only pharmacological treatment so far and might improve 28-day survival, but not beyond this period. However, around 50% of patients will not benefit from corticosteroid treatment and these patients have a 70% mortality rate over 6 months. These figures illustrate the need for more effective pharmacological treatments, which are currently under investigation and are summarized by Jef Verbeek and colleagues.

Non-alcoholic fatty liver disease (NAFLD) is a collective noun for different stages of fatty liver disease (ranging from isolated steatosis to inflammation, fibrosis and cirrhosis) in the co-existence of other dysmetabolic features such as insulin resistance and obesity. In the last decade, insight in the pathophysiology of NAFLD increased exponentially. In parallel, evidence supporting the efficacy of life style interventions (including diet modification and physical exercise) and bariatric surgery was established and implemented in clinical practice guidelines by our hepatology societies. Emmanuel Tsochatzis and colleagues provide an overview on the current **treatment options for NAFLD**. However, the increased knowledge on NAFLD pathophysiology did not lead to the availability of an effective and approved drug yet. Given its high prevalence and health burden, collaborative efforts between academic researchers and pharmaceutical industry boosted the drug development pipeline for NAFLD. Many clinical trials are ongoing, but unfortunately also many clinical trials failed. This probably is related to the pathophysiological complexity and heterogeneity of NAFLD and the need of

surrogate end-points in clinical trials given the rather slow natural course of the disease. Mohammed Eslam and colleagues provide insight in the **quest for effective drugs to treat NAFLD** and its different molecular targets.

Strikingly, alcohol-related liver disease and NAFLD, the two most prevalent liver diseases, are both primarily life-style related. This reflects the need for a combined strategy of effective implementation of life-style interventions, pharmacological approaches and preventive strategies on societal and health care level. In addition to life style and metabolic co-morbidities, genetic background determines the risk to develop advanced liver disease in the context of NAFLD. One in four adults in the general population have NAFLD, but not all of them will develop advanced liver disease. Luca Valenti and colleagues discuss the potential of **polygenic risk scores** in disease detection and prediction of the risk of progression to severe forms. This approach might pave the way for tailored follow-up and treatment of NAFLD patients.

The global prevalence of viral hepatitis B and C remains high, especially in the Asian and African region. The discovery and availability of new direct-acting antivirals against hepatitis C was probably the most important game-changer in hepatology in the last decade. These well-tolerated, oral drugs show eradication rates above 95% after a relatively short treatment period of several weeks. In contrast to hepatitis C, we manage to pharmacologically suppress hepatitis B in patients, but eradication is rare. Markus Cornberg and colleagues review the current developments in new therapies aimed at **hepatitis B** cure. Hepatitis D is a virus that only exists in the presence of hepatitis B and this co-infection causes the most severe form of chronic viral hepatitis. The prevalence of **hepatitis D** is higher than previously considered, however an effective therapy is lacking. George Papatheodoridis and colleagues summarize the current status of the epidemiology, diagnosis and treatment of hepatitis D infection.

Viral hepatitis and other chronic liver diseases can lead to hepatocellular carcinoma, which is the most prevalent primary liver cancer. Treatment options are dependent on the disease stage, underlying liver function and performance state of the patient. Unfortunately, the majority of patients are diagnosed when curative treatments such as resection, ablation or liver transplantation are not feasible anymore. Maria Reig and colleagues provide an overview on the rapidly evolving field of pharmacological treatment options for **hepatocellular carcinoma**.

Primary sclerosing cholangitis (**PSC**) is a rare immune-mediated cholestatic disease. Its prevalence is relatively highest in Northern Europe and Northern America. For example, in the Nordic Liver Transplant Region (Norway-Sweden-Denmark-Finland-Estonia) PSC is the most frequent indication for liver transplantation. It is an important cause of bacterial cholangitis, portal hypertension, cirrhosis and liver malignancy and 75% of PSC patients have inflammatory bowel disease. Although ursodeoxycholic acid is often prescribed, no medical therapy has been firmly shown to slow disease progression of PSC yet. Palak Trivedi and colleagues discuss the current platform of interventional trials in PSC and its potential molecular targets.

Alpha-1-antitrypsin (A1AT) is a protein synthesized mainly by the liver. A1AT deficiency is caused by mutations in the SERPINA1 gene, leading to the synthesis of aberrant forms of A1AT that accumulate in the liver and leading to a lack of normal and protective A1AT in the circulation and lungs. Therefore, patients with A1AT deficiency are at risk for liver

and lung disease. No pharmacological agents for the liver exist. Interestingly, new drugs are in development of which RNA interference therapy by subcutaneous injections is so far the most promising one. Pavel Strnad and colleagues summarize the current approaches silencing **A1AT** production, improving protein folding and secretion or promoting A1AT degradation.

Finally, Andrea de Gottardi and colleagues provide a practical overview on when and how to use **direct oral anticoagulants (DOACs)** in patients with advanced chronic liver disease. DOACs emerged as valid alternatives to traditional anticoagulants. However, liver dysfunction, renal insufficiency and the balance between increased risk of thromboembolism and bleeding in liver patients need to be taken into account when prescribing these drugs.

We deeply thank all the leading experts and their team members who contributed to this special issue and we thank the editorial board of COPHAR for providing us this stage. Together, we hope that this collection of articles raises the awareness for liver diseases and inspires people within and outside the hepatology field to improve the outcomes of our patients with chronic liver disease.