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Overcoming the roadblocks in hepatitis C virus infection

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According to the WHO more than 170 million people are infected with the hepatitis C virus (HCV), causing a slowly fibrosing hepatitis that subsequently can lead to cirrhosis and its sequelae. Chronic hepatitis C is one of the most common causes of liver disease and cancer world-wide.

The development of direct-acting antivirals (DAAs) has revolutionized HCV treatment by offering genuine prospects for the first comprehensive cure of a chronic viral infection in man [1]. This unprecedented success is due to important scientific, clinical, and regulatory developments [1] and has resulted in novel treatment approaches, rapidly changing the management of HCV-infected patients [2].

25 years following the discovery of the virus, the Journal takes the opportunity to highlight milestones in basic science and clinical developments and review the remaining challenges in the prevention and treatment of HCV infection. The discovery of the virus, using an expression cloning approach, the characterization of its genome and life cycle, and the development of novel model systems have provided the base for the development of DAAs and complementary therapeutic approaches. Dr. Cosset and Dr. Dubuisson are reviewing the latest discoveries in the molecular virology of HCV infection. HCV infection has been proven to be a unique model to understand the mechanism of viral evasion and how the virus enables persistent infection. Dr. Thimme and Dr. Heim present an overview on previous and new findings in antiviral innate and adaptive immune responses and how these are interrelated. Dr. Lauer, Dr. Baumert and colleagues present how this knowledge can be applied to develop a vaccine and which challenges remain to accomplish this important task. A key challenge for vaccine development and for understanding the pathogenesis of HCV-induced liver disease is the lack of suitable animal models. Dr. Meuleman and colleagues highlight what has been accomplished so far and discuss the next challenges for the development of disease biology models.

The clinical investigation of the disease has led to a better understanding of its natural course as well as its association with comorbidities. The data on the natural course of hepatitis C virus infection (including aspects of spontaneous or treatment-induced resolution) are presented in this Supplement by Dr. Dusheiko and Dr. Westbrook. HCV infection is one of the leading causes of hepatocellular carcinoma worldwide. Emerging data suggest that viral cure reduces but does not eliminate the risk for HCC development. Dr. Hoshida, Dr. Chung and colleagues review the mechanisms of HCC pathogenesis and perspectives on how to prevent this lethal disease. Hepatitis C virus infection and a number of comorbidities are considered to be interrelated. Dr. Negro provides a comprehensive overview on facts and fictions in this clinically important field.

The development of interferon-free all oral combination therapies for hepatitis C represents one of the fastest revolutions in medicine ever [1,2]. Generally, two distinct strategies are pursued: one with and others without a nucleosidic polymerase inhibitor. The nucleoside polymerase inhibitor sofosbuvir was successfully combined in a step-up process with NS3/4A protease inhibitors, NS5A-inhibitors, and non-nucleosidic polymerase inhibitors plus or minus ribavirin. A fixed drug combination, consisting of sofosbuvir and the NS5A-inhibitor ledipasvir, has completed phase 3 trials in treatment-naive and experienced patients and achieved sustained virologic response rates above 95%. All relevant clinical trials are summarized by Dr. Jacobson and Dr. Kumar. The second strategy combines all drug classes but nucleosidic polymerase inhibitors – NS3/4A protease inhibitors, NS5A-inhibitors, non-nucleosidic polymerase inhibitors and ribavirin – in a step-down process. The combination of ritonavir-boosted ABT-450, with ombitasvir, dasabuvir and ribavirin also achieved sustained virologic response rates above 95% both in treatment-naive as in treatment-experienced patients with chronic hepatitis C. This and other studies without a nucleosidic polymerase inhibitors are summarized in this Supplement by Drs. Welzel, Dultz, and Zeuzem.

The most challenging treatment approach is resembled by previously difficult to cure patients (decompensated cirrhosis, patients under immunosuppressive therapy, co-infected patients, etc.). The management of HCV/HIV coinfected patients is presented by Dr. Sulkowski, while Dr. Forns and colleagues summarize the current knowledge on how to manage and treat

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patients with decompensated cirrhosis as well as patients pre- and post-transplantation. A key challenge is access to treatment, Dr. Ford, Dr. Wiktor and colleagues review how to promote access to treatment through evidence based recommendations. Basis for this approach is the detailed understanding of the global epidemiology and genotype distribution of the hepatitis C virus, which in this Supplement is comprehensively summarized by Dr. Razavi and colleagues.

The Editors of this Supplement are convinced that the most important aspects in the field of hepatitis C are covered by leading experts in the field and that the manuscripts provide a comprehensive overview on the current knowledge and are state-of-the-art.

Conflict of interest

S. Zeuzem has consultancies for AbbVie, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead, Idenix Janssen, Merck, Novartis, Roche, Santaris, and Vertex. T. Baumert, has nothing to declare.

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