

# Contents

<b>Preface</b>	<b>xiii</b>
Paul J. Pockros	
<b>Novel Interferons for Treatment of Hepatitis C Virus</b>	<b>351</b>
Virginia Clark and David R. Nelson	
<p>The current standard of care for treatment of hepatitis C is pegylated interferon and ribavirin. Despite the large number of new oral agents under development, interferon will likely remain the backbone of future therapy. Interferon has unique antiviral and immunomodulatory properties, which have been critical in limiting resistance to protease inhibitors and improving efficacy. Hence, optimizing pharmacokinetics and promoting adherence to interferon dosing regimens will become even more critical as new regimens enter the clinical arena. This review highlights novel interferons under development that may offer therapeutic advantages over the formulations currently available.</p>	
<b>Antifibrotics for Chronic Hepatitis C</b>	<b>365</b>
Paul J. Pockros	
<p>Development and testing of antifibrotic agents for the treatment of chronic hepatitis C have generally been targeted toward hepatic stellate cells, transforming growth factor-<math>\beta</math>, the inflammatory response, or extracellular matrix accumulation. Although several agents such as interferon-<math>\gamma</math>, long-term pegylated interferon, and caspase inhibitors have been studied, none have proved to be effective to date. There is a clear need for drugs that inhibit or reverse hepatic fibrosis as these would be immediately applicable to patients for whom antiviral therapy has failed or who have contraindications to antiviral therapy such as those with decompensated liver disease or renal failure. A major impediment in the development of new drugs in this field has been the inability to identify appropriate histologic or clinical end points within a reasonable period of study. Progress on providing suitable end points to therapy will then promote the development of newer agents.</p>	
<b>Antisense Inhibitors, Ribozymes, and siRNAs</b>	<b>375</b>
Alexander J.V. Thompson and Keyur Patel	
<p>The current standard of care for the treatment of hepatitis C virus infection, pegylated interferon-<math>\alpha</math> and ribavirin, is costly, associated with significant side effects, and effective in only 50% of patients. There is therefore a need for the development of novel antiviral therapies. One such approach involves the application of gene silencing technologies, including antisense oligonucleotides, ribozymes, RNA interference, and aptamers. However, despite great scientific advances over the past decade, and promising in vitro data, several significant challenges continue to limit</p>	

the translation of this technology to the clinical setting. This review provides a concise update of the current literature.

### **Hepatitis C Virus Infection and Immunomodulatory Therapies**

391

Kimberly A. Forde and K. Rajender Reddy

Hepatitis C virus (HCV) infection remains a large-scale and significant health concern. The combination of subcutaneously administered pegylated interferon and oral ribavirin is the FDA-approved regimen for the treatment of chronic HCV infection. Combination therapy may result in a sustained virologic response leading to HCV eradication, with a reduction in risk for cirrhosis, hepatic decompensation, and hepatocellular carcinoma.<sup>9,10</sup> However, the combination of PEG-IFN and ribavirin does not universally result in cure in all patients who undergo treatment. In this article, the authors discuss immunomodulatory therapies and clinical trials in the treatment of HCV infection.

### **Cyclophilin Inhibitors**

403

Philippe A. Gallay

The percentage of patients chronically infected with hepatitis C virus (HCV) who have reached sustained antiviral response has increased since the introduction of the pegylated interferon-alpha (pIFNa) and ribavirin (RBV) treatment. However, the current standard pIFNa/RBV therapy not only has a low success rate (about 50%) but is often associated with serious side effects. Thus, there is an urgent need for the development of new anti-HCV agents. Cyclophilin (Cyp) inhibitors are among the most promising of the new anti-HCV agents under development. Recent clinical studies demonstrate that Cyp inhibitors are potent anti-HCV drugs, with a novel mechanism of action and efficacy profiles that make them attractive candidates for combination with current and future HCV treatments.

### **Ribavirin Analogs**

419

William W. Shields and Paul J. Pockros

Ribavirin is ineffective against hepatitis C virus as mono-therapy but is critical in attaining both early virologic response and sustained virologic response when combined with pegylated interferon. Ribavirin has significant dose-limiting toxicities, the most important of which is hemolytic anemia. Taribavirin is a ribavirin pro-drug, which targets the liver and has less incidence of anemia, and it may be a promising alternative to ribavirin in the future.

### **Boceprevir, an NS3 Protease Inhibitor of HCV**

429

Kenneth Berman and Paul Y. Kwo

Hepatitis C virus (HCV) is a major cause of chronic liver disease leading to death from liver failure or hepatocellular carcinoma. Hepatitis C is the most

common indication for liver transplantation worldwide and is a major cause of the increased incidence of hepatocellular cancer in the United States. The current paradigm for HCV treatment relies on pegylated interferon and ribavirin as agents that enhance endogenous mechanisms for viral clearance and are dependent on host factors. In patients with genotype 1 HCV infection, sustained viral response (SVR) rates remain suboptimal, with less than half of genotype 1–infected individuals going on to achieve SVR. This has led to a shift in the investigational focus for treatment of HCV toward specifically targeted antiviral therapy for HCV agents. This review focuses on boceprevir, a protease inhibitor, and discusses its mechanism of action, effects on HCV, and viral resistance.

### **Telaprevir: Hope on the Horizon, Getting Closer**

441

Ilan S. Weisberg and Ira M. Jacobson

Standard therapy with pegylated interferon and ribavirin for chronic hepatitis C is effective in 40% to 50% of individuals with genotype 1 hepatitis C virus (HCV) infection and is associated with significant treatment-related toxicities. Newly developed small molecules that target key enzymes essential for HCV replication are in development. Telaprevir, a peptidomimetic inhibitor of the HCV NS3/4A protease, has shown great promise in early trials and is currently in advanced stages of clinical development. In treatment-naïve patients and those with previous treatment failure, the addition of telaprevir to standard interferon and ribavirin therapy is well tolerated and enhances rates of sustained virologic response while shortening the treatment duration. In this report, the current experience using telaprevir to treat chronic HCV infection as monotherapy and in combination with other agents is reviewed.

### **HCV NS5B Polymerase Inhibitors**

453

James R. Burton, Jr. and Gregory T. Everson

Chronic hepatitis C virus (HCV) infection affects approximately 4 million persons and is the major indication for liver transplantation in the United States. The current standard for treatment of HCV is pegylated interferon in combination with ribavirin. Despite significant advances in treatment, only approximately 50% of patients of treated patients clear HCV infection. Polymerase inhibitors, given their potent antiviral effects, represent a major contribution to the future of HCV treatment. Whether these new drugs will have a role in the treatment of the difficult patient (non-responders, those co-infected with HIV, decompensated liver disease and liver transplant recipients) remains to be determined.

### **Caspase Inhibitors for the Treatment of Hepatitis C**

467

Howard C. Masuoka, Maria Eugenia Guicciardi, and Gregory J. Gores

Decreasing hepatocyte injury and death is an attractive therapeutic target in chronic hepatitis C and other liver diseases. Apoptotic cell death is a critical mechanism responsible for liver injury in hepatitis C, and contributes to

hepatic fibrogenesis. At the cellular level, apoptosis is executed by a family of cysteine proteases termed caspases. Caspase inhibitors have been developed to inhibit these proteases and attenuate cellular apoptosis *in vivo*. By reducing hepatocyte apoptosis these agents have the potential to serve as hepatoprotective agents, minimizing liver injury and fibrosis. Studies on a variety of animal models, and time-limited studies in human patients with hepatitis C suggest these are promising therapeutic agents. However, although these agents hold promise, their usefulness requires further studies, especially longer duration studies using hepatic fibrogenesis as the end point before they can be considered further for the treatment of patients infected with the hepatitis C virus.

### **Monoclonal and Polyclonal Antibodies Against the HCV Envelope Proteins**

477

Heshaam M. Mir, Aybike Bircerdinc, and Zobair M. Younossi

The potential for developing efficient and efficacious therapies for hepatitis C virus continues to improve. Insight into the molecular processes involved in attachment, entry, and fusion suggests that antibodies could potentially inhibit viral replication at any or all of these stages, and the attachment and entry stages present the best target for antibodies that can attack the virus. Monoclonal and polyclonal antibodies present an important therapeutic option in this area, and this article assesses current investigations of several antibodies.

### **Thrombopoietin Agonists for the Treatment of Thrombocytopenia in Liver Disease and Hepatitis C**

487

Geoffrey Dusheiko

Thrombocytopenia is a condition of unusually low level of platelets in blood, resulting from an imbalance between the production and destruction of platelets, and is associated with aplastic anemia, myelodysplasia, and idiopathic thrombocytopenic purpura (ITP). Thrombocytopenia can also be associated with severe chronic liver disease as a result of several factors that may act in concert, including reduced production of the endogenous thrombopoietic growth factor, thrombopoietin (TPO). This article examines the nature of thrombocytopenia, ITP, and TPO.

### **Index**

503