Preface xiii
Fred Poordad

1990–2010: Two Decades of Interferon-Based Therapy 473
Maria Buti and Rafael Esteban

Twenty-five years have passed since interferon-a was first used in the treatment of chronic hepatitis C infection, and even now it remains an essential part of the standard of care for this condition. At present, the recommended treatment is a combination of pegylated interferon and ribavirin A. There have been enormous advances in our understanding of the mechanisms through which interferon works and in identifying factors related to the response to this treatment. Even with the development of new protease inhibitors, it is likely that interferon will remain an essential component of hepatitis C treatment.

Naives, Nonresponders, Relapsers: Who Is There Left to Treat? 483
Archita P. Desai and Nancy Reau

Hepatitis C has a high prevalence in the United States, and the disease burden of HCV will increase over the next 20 to 30 years by many estimates. Trials to evaluate new therapies and optimize the use of triple drug therapies are needed if HCV is to be successfully controlled and its incumbent morbidity and mortality drastically lowered for all groups of patients. With improvements in ability to achieve SVR with agents such as telaprevir and boceprevir, efforts to improve treatment uptake rates and to re-examine the utility of universal or more inclusive screening for chronic hepatitis C are warranted.

Redefining Baseline Demographics: The Role of Genetic Testing in Hepatitis C Virus Infection 497
Jacinta A. Holmes, Paul V. Desmond, and Alexander J. Thompson

The current standard of care for hepatitis C virus (HCV) infection is pegylated interferon and ribavirin. Unfortunately, treatment cures at best only 40% to 50% of patients infected with genotype 1 HCV, the most common HCV genotype in Western countries. Treatment is also expensive and is often poorly tolerated. Therefore, the identification of patients most likely to benefit from treatment is clinically important. Genome-wide association studies have recently identified genetic variants, most notably IL28B and ITPA, which will enhance the ability of clinicians to personalize antiviral therapy for HCV infection.

An Overview of Emerging Therapies for the Treatment of Chronic Hepatitis C 515
Jawad A. Ilyas and John M. Vierling

Chronic hepatitis C (CHC) is a leading cause of chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC) worldwide. Currently,
pegylated interferon (Peg-IFN) and ribavirin therapy achieve curative responses in 40% to 80% of patients, depending on genotype. Recognition of new therapeutic targets for HCV therapy has led to development of novel therapies. The purpose of this review is to summarize the status of novel therapeutics for CHC that promise to increase the safety and efficacy of therapy.

**Boceprevir: A User's Guide**

Paul Y. Kwo and Rong Zhao

Given its essential role in the process of hepatitis C virus (HCV) replication, the viral NS3/4A serine protease is arguably the most thoroughly characterized HCV enzyme and the most intensively pursued anti-HCV target for drug development thus far. Recent data have demonstrated promise for the NS3 protease inhibitor boceprevir, which, when added to the standard of care peginterferon and ribavirin, improves sustained virological response while shortening duration of therapy in genotype-1–infected individuals. This review discusses the mechanism of action of boceprevir, its effects on HCV, and its viral resistance.

**Telaprevir User's Guide**

AnnMarie Liapakis and Ira Jacobson

For a decade, standard therapy for patients with genotype 1 chronic HCV (HCV G1) consisted of pegylated interferon (Peg-IFN) alfa-2a or Peg-IFN alfa-2b, combined with ribavirin. Despite the improved efficacy of this therapy over others, the overall sustained virologic response rate in patients with HCV G1 was still low. This article discusses phase I, II, and III trials examining telaprevir's role in treating patients with HCV. We have now entered an era of combination therapy utilizing direct acting anti-virals, the start of which was marked by the FDA approval of HCV protease inhibitors.

**Management of the Treatment-Experienced Patient Infected with Hepatitis C Virus Genotype 1: Options and Considerations**

Omer Khalid and Bruce R. Bacon

Individuals infected with hepatitis C virus (HCV) are at risk for cirrhosis and/or hepatocellular carcinoma. Treatment of HCV infection has undergone several revisions over the past 15 years and continues to evolve. The current major advance is with the protease inhibitors in addition to pegylated interferon and ribavirin. The emergence of resistance needs to be monitored carefully as newer and more potent drugs are added to the interferon and ribavirin backbone drugs. In addition, adverse events will be more frequent and some novel ones will require special attention.

**The HIV/HCV-Coinfected Patient and New Treatment Options**

Marie-Louise C. Vachon and Douglas T. Dieterich

Hepatitis C (HCV) treatment is on the cusp of change with the approval of the first direct-acting antivirals: telaprevir and boceprevir. Drug–drug interactions with HIV antiretrovirals, increased toxicity, and rapid selection of HCV-resistant mutants are among the treatment complexities expected
in this difficult-to-treat population. Until the current standard of care changes, focus should be on strategies to optimize management of HIV/HCV-coinfected patients with currently available options. This article reviews the latest predictive factors of response to HCV treatment with the current standard of care in HIV-coinfected patients, and new treatment options.

**Second-wave Protease Inhibitors: Choosing an Heir**

Sandra Ciesek, Thomas von Hahn, and Michael P. Manns

Infection with the hepatitis C virus (HCV) is a major cause of chronic liver disease and a leading indication of liver transplantations worldwide. The current standard of care for chronic hepatitis C is a combination of pegylated interferon-α and ribavirin that is effective in slightly more than half of cases and is associated with significant side effects. The first directly acting antivirals recently reached the US market, but will have shortcomings that should in part be overcome by the second-wave PIs that are in development. This article gives an overview of the compounds that will soon be available.

**The HCV NS5B Nucleoside and Non-Nucleoside Inhibitors**

Fernando E. Membreno and Eric J. Lawitz

This article introduces one of the most diverse classes of direct-acting antivirals for hepatitis C, the nucleoside and non-nucleoside NS5B polymerase inhibitors. Through a systematic review of the published literature, we describe their structure, mechanism of action, issues with resistance, and clinical effectiveness shown in the latest clinical trials. Direct-acting antiviral combination trials that have already shown some early promising results even in the setting of interferon-sparing antiviral regimens are discussed.

**The NS5A Replication Complex Inhibitors: Difference Makers?**

Robert G. Gish and Nicholas A. Meanwell

The development and approval of direct-acting antiviral agents looks set to transform the treatment of chronic hepatitis C infection. Among the agents in development are novel compounds that inhibit the function of the NS5A protein: a pleiotropic protein with a complex and essential role in viral replication. Preclinical studies have demonstrated the potency of these agents across a broad range of viral genotypes, and in early phase trials, they rapidly suppressed viral replication when administered as monotherapy or in combination with pegylated interferon-α and ribavirin. The discovery and development of NS5A replication complex inhibitors is summarized in this review.

**Hepatitis C Therapy: Other Players in the Game**

Joseph Ahn and Steven L. Flamm

Therapies in addition to the direct-acting antiviral agents (DAA) under evaluation for chronic hepatitis C include host targets such as cyclophilin inhibitors and immunomodulators. Both passive and therapeutic vaccines hold
promise for the future. Although the numbers of drug categories and individual agents are increasing, only a handful of the non-DAAs seem to be ready to move on to phase III trials. New interferon agents are in development, and ribavirin variants are still under consideration. The role of the other players in the overall armamentarium against hepatitis C virus is still evolving.

**Mixing and Matching Drugs: What Makes Sense?** 657

Tania M. Welzel and Stefan Zeuzem

The introduction and ongoing development of directly acting antiviral agents (DAAs) and drugs targeting host cell structures will change the management of patients with chronic hepatitis C virus (HCV) infection. The concomitant use of the protease inhibitors telaprevir or boceprevir with the standard of care, a combination of pegylated interferon (PegIFN) and ribavirin, will represent the new standard for the treatment of HCV genotype 1 infection. Contraindications and side effects limit the applicability of interferon-based therapies and motivate the investigation of PegIFN-sparing regimens. Different DAA combinations under investigation are reviewed in this article.

**Interferon-Free Regimens: The Near Future, the Likely and the Not So Likely** 665

Mitchell L. Shiffman

Remarkable progress has been achieved in the treatment of chronic hepatitis C virus (HCV) since interferon was first used to treat this pathogen more than 20 years ago. This article reviews the mechanisms through which interferon is believed to suppress HCV and lead to SVR. These observations are used to speculate as to whether an all-oral antiviral cocktail could “cure” HCV in the near future.

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