
Preface

I first began caring for patients with chronic hepatitis C virus (HCV) and participating in clinical trials to treat this virus in 1990. I distinctly remember enrolling my first patients with non-A, non-B hepatitis into a clinical trial in which they received either standard interferon alfa-2 α 1, 3, or 5 million IU or a placebo injection three times weekly. Standard interferon had not yet been approved by the Food and Drug Administration for treatment of non-A, non-B hepatitis (HCV). The HCV had just been identified when this trial was initiated and no tools were yet available to measure HCV RNA. The entry criteria were based on having a serum level of alanine aminotransferase (ALT) at least 1.5 times the upper limit of normal, and the end point was a biochemical response defined as normalization of serum ALT. We were ecstatic when we realized that 12% of patients who received active drug had achieved a sustained virologic response.

Over the next 2 decades, my staff and I participated in numerous clinical trials designed to either slow fibrosis progression and/or improve sustained virologic response (SVR) and “cure HCV.”

During this time, naming studies became fashionable and having a good name became almost as important as having a good study design. Some of the more memorable studies my team and I participated in, either because of their clinical significance or simply because the study had a good name (listed in alphabetical order), included the following: 007, 107, ACCELERATE, ACHIEVE, ELEVATE, ENHANCE, HALT-C, IDEAL, NCORE, PROVE, SPRINT, STEALTH-C3, REALIZE, and RESPOND. Although many of the studies we participated in were unsuccessful, each taught us a bit more about this virus, its natural history, and how to treat it more successfully. Over the years, a slow stepwise increase in SVR rates did occur. However, these steps paled in comparison to the magnificent success we have finally realized with the development of HCV direct-acting antiviral agents. As this book goes to press, the first two HCV protease inhibitors, boceprevir and telaprevir, have been approved by the Food and Drug Administration. When either of these protease inhibitors is utilized along with peginterferon and ribavirin to treat chronic HCV, an SVR can be achieved in up to 80% of patients. Our ability to “cure” HCV has increased sevenfold in just 20 years.

I am truly grateful to the thousands of patients who have entrusted me with their care and for many, their willingness to enroll into one or more of the hundreds of clinical trials I have directed during this time. Our mutual goal to

develop treatments which will “cure” HCV in all persons infected with this virus is on the brink of becoming reality.

This book chronicles the advances we have made in our understanding of chronic HCV and the various methods we have utilized to try and eradicate this virus. The title was selected because these “Advances in Treatment” will soon enable us to make good on our “Promise for the Future” and “cure” HCV in the vast majority of our patients.

I am extremely grateful to my friends and colleagues who agreed to contribute to this project. The hard work and thought that these outstanding clinicians and scientists have put into their contributions is clearly evident. The book is composed of 25 chapters divided into four parts.

Part 1 The Natural History of Chronic HCV

This part starts off with an outstanding summary of the epidemiology of chronic HCV, how the epidemic started, where we are now, and what may happen in the future. The chapter on acute HCV looks at risk factors for acquiring HCV, why and how spontaneous resolution occurs, and the impact of treating HCV soon after the onset of infection. Other chapters in this part deal with tools to assess fibrosis progression to cirrhosis, the impact of hepatic steatosis, the role of HCV and its treatment on the development of hepatocellular carcinoma, how HCV and its treatment affects extrahepatic organs, HCV in persons coinfecting with HIV, and how HCV impacts patients with chronic renal failure and the limitations of our current treatment in this population. This part concludes by discussing the impact of treatment on the natural history of chronic HCV.

Part 2 Treatment of Chronic HCV with Interferon-Based Therapy

This part starts by reviewing the development of interferon and ribavirin for treatment of chronic HCV and whether these agents will remain the backbone for all future therapies. The next chapter evaluates how immune modulators have been explored as a treatment for HCV and whether there will be a role for such agents in the future. The next several chapters deal with assays to measure HCV RNA and how to assess viral response, the concepts of response-guided therapy and how this concept could be utilized to maximize SVR rates, tips on how to manage the side effects of peginterferon and ribavirin, how host genetics affect response to peginterferon and ribavirin, and how genetic testing could be utilized to guide treatment decisions in the future. The final chapter in this part deals with maintenance peginterferon therapy as a treatment for chronic HCV; why this treatment was conceived and why this approach failed to meet our expectations.

Part 3 Antiviral Therapy for Chronic HCV

This part starts by reviewing the various cellular and viral targets which could be utilized to attack HCV. The second chapter discusses viral resistance, how this could emerge during HCV treatment, and the possible long-term impact of mutations which develop within the hepatitis C viral genome. The data which led to the approval of boceprevir and telaprevir for treatment of chronic HCV and preliminary data on future protease and polymerase inhibitors are then reviewed. The final two chapters in this part deal with whether we will ever be able to “cure” HCV without peginterferon and ribavirin and if not whether oral antiviral agents will be utilized as a maintenance cocktail to control HCV and prevent fibrosis progression in the future.

Part 4 Liver Transplantation for Chronic HCV

The final part of the book deals with issues related to liver transplantation. Cirrhosis and hepatocellular carcinoma secondary to chronic HCV are collectively the leading indication for liver transplantation in most countries. The first two chapters in this part review the natural history of chronic HCV following liver transplantation, and discuss whether HCV positive organs could be utilized for transplantation now or in the future when antiviral agents might be able to suppress or eradicate HCV. The final two chapters deal with treating HCV in patients prior to and or following liver transplantation and the impact that oral antiviral agents will have in these settings.

It is my hope that you will find *Chronic Hepatitis C Virus: Advances in Treatment: Promise for the Future* a useful addition to your reference collection. The historical perspective provides a very nice summary of the obstacles we have overcome to improve our treatments of this virus. I am hopeful that the projections made by many of the contributors will become reality and our promise for the future will be realized.

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