Direct-Acting Antiviral Agents

Regimens for the Interferon Failure Patient

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KEYWORDS

• Hepatitis C • Direct-acting antivirals • Interferon • Treatment

KEY POINTS

- There are multiple reasons why patients failed interferon-containing treatments in the past, including intolerability to interferon, ineffective response to interferon, and relapse after treatment.
- With the emergence of new direct-acting antiviral agents (DAAs), there are multiple treatment options available to patients who have previously failed interferon-containing regimens.
- Hepatitis C genotype and severity of disease guide therapy choices in patients who have failed prior therapy.

INTRODUCTION

The treatment of hepatitis C has evolved dramatically since the historic days of exclusively interferon-containing therapy regimens and has continued to change rapidly since the initial introduction of direct-acting antiviral therapy in 2011. With the advent of multiple new treatment regimens, there are options for treatment now available to patients who previously failed interferon-containing therapy. Most of these regimens do not contain interferon, although in a few situations, interferon in combination with DAAs is still recommended for treatment. Most of the new drug regimens are highly effective and have minimal side effects, providing a dramatic improvement in tolerance and outcome of treatment on the course of the disease.

HISTORY OF INTERFERON-CONTAINING REGIMENS

Until recently, interferon-alfa combined with ribavirin was the mainstay of treatment of hepatitis C. In 1990, Hoofnagle and colleagues[1] demonstrated utilization of interferon

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alone for hepatitis C, which at the time was termed, *non-A, non-B hepatitis*. Interferon-alfa had been previously demonstrated to have a wide spectrum of antiviral activity against other viruses and was a "natural choice" as an initial therapeutic agent for hepatitis C. In this study, 10 patients were treated for a total of 12 months, and although 8 of 10 responded initially, only 10% of the study cohort demonstrated sustained virologic response (SVR) 1 year after treatment. In 2001, pegylated interferon was proposed as an alternative to interferon-alfa. The pegylated form of the drug has a covalently attached polyethylene glycol compound, which delays protein clearance and reduces immunogenicity, thereby resulting in a longer half-life of the drug, improved efficacy, and less frequent dosing. The properties of pegylated interferon allow for a decrease in adverse effects compared with standard interferon and improved patient adherence.[2] A randomized controlled trial comparing the pegylated form to interferon-alfa demonstrated increased SVR to up to 49% in the high-dose treatment group. The adverse effect profile was similar to interferon-alfa despite an increased SVR.[3]

Although ribavirin was initially proposed as potential therapeutic drug for hepatitis C in 1991[4] and used in combination with interferon-alfa in 1996 (improving SVR rates to 40%), it was not until 2001 that the first randomized controlled trial was performed by Manns and colleagues,[3] examining the synergistic effect of ribavirin with pegylated interferon in the treatment of hepatitis C. Patients were treated for 48 weeks, and SVR for patients treated with the combination of pegylated interferon and ribavirin increased to 54%, with SVR rates of approximately 80% in patients with genotypes 2 and 3. Subsequently, recommendations for the treatment of hepatitis C consisted of a combination of pegylated interferon and weight-based ribavirin for all patients with hepatitis C. Although these SVR rates were higher than previously reported, there was a significant amount of nonresponse to interferon-containing regimens in the real world.

Ten years later, the first generation of DAAs was discovered and integrated into clinical practice, in combination with pegylated interferon and ribavirin. Boceprevir and telaprevir were the first DAAs, both protease inhibitors, and were studied in the SPRINT-1 (Serine Protease Inhibitor-1), SPRINT-2 (Serine Protease Inhibitor-2), RESPOND-2 (Retreatment with HCV Serine Protease Inhibitor Boceprevir and Pegintron/Rebetrol 2), ILLUMINATE (Illustrating the Effects of Combination Therapy with Telaprevir), PROVE (Protease Inhibition for Viral Evaluation), and REALIZE (Retreatment of Telaprevir Based Regimen to Optimize Outcomes) studies.[5–9] These agents were approved in 2011 for the treatment of exclusively genotype 1 hepatitis C infection. Treatment with these agents in conjunction with pegylated interferon and ribavirin significantly increased SVR rates to up to 75% in treatment-naïve patients. Patients who were treated previously, however, had mixed results. Although prior treatment relapsers had response rates of 69% and 88%, prior partial responders had response rates of 40% and 59%, and prior null responders had response rates as low as 23% to 38%. There was, therefore, limited efficacy of these agents in patients who had been treated previously. In addition, these agents unfortunately were associated with severe side effects (severe anemia and rash), often worse than with pegylated interferon and ribavirin alone. They were associated with high pill burdens and restrictions on administering the medications with very high-fat meals and had low efficacy and safety in treatment-experienced patients. Most recently, several other DAAs have been developed and approved for use, thus broadening treatment options in patients who have previously failed interferon-containing regimens.

INTERFERON INTOLERABILITY

Prior to the discovery of DAAs for treatment of hepatitis C virus (HCV), treatment consisted of 24 to 48 week regimens of pegylated interferon and ribavirin. These