Next-Generation Regimens

The Future of Hepatitis C Virus Therapy

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KEYWORDS

• Hepatitis C • Genotype 1 • Direct-acting antivirals • Second generation
• Resistance-associated variants

KEY POINTS

- The rapid developments in therapy for hepatitis C have been historic, and have ushered in a new paradigm for the treatment of hepatitis C.
- Although prior therapeutic regimens were limited by efficacy, tolerability, genotype specificity, and duration of therapy, numerous improved agents are in development.
- Optimal combinations should facilitate a fixed duration of therapy for all patient subtypes.

INTRODUCTION

The treatment of chronic hepatitis C virus (HCV) has undergone a recent phase of rapid evolution. At the present time, 3 interferon (IFN)-free direct-acting antiviral (DAA) regimens are approved for the treatment of HCV genotype 1. Within the next few years, continued development of novel agents and combinations is expected, with the aim of coming closer to the ideal regimen. This article focuses on future therapeutic options for HCV with an emphasis on drug development and key ongoing trials.

LIMITATIONS OF PAST REGIMENS

Prior to the DAA era, HCV treatment was limited by the adverse effect profile and poor efficacy of IFN/ribavirin (RBV)-based regimens. Although the advent of DAAs has

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brought marked improvements in tolerability and efficacy, current therapies remain limited by variable durations of therapy ranging from 8 to 24 weeks and genotype specificity. Future regimens should target these limitations.

PHASE III TRIALS

Daclatasvir/Asunaprevir/Beclabuvir

Phase III data for another oral DAA regimen expected to reach the US market have been reported. Combination daclatasvir (30 mg daily), asunaprevir (200 mg daily), and beclabuvir (75 mg daily) in a twice-daily fixed dose (DCV-TRIO) was administered to 415 treatment naïve and experienced (pegylated interferon [PEG-IFN]/RBV), noncirrhotic genotype patients for 12 weeks, dubbed UNITY-I.[1] SVR12 was comparable for treatment-naïve and experienced patients (91% vs 89% respectively) regardless of baseline HCV RNA level or interleukin (IL)28 b genotype. When stratified by subgenotype, G1b patients were more likely to achieve SVR than G1a patients regardless of prior treatment exposure (98% vs 90% for naïve patients and 100% vs 85% for experienced patients). This study did not include RBV; however, one of the currently approved regimens that includes a protease inhibitor, NS5A inhibitor, and nonnucleotide polymerase inhibitor demonstrated superior rates of SVR (90% vs 96%) in G1a patients when RBV was included.[2] DCV-TRIO was well tolerated, with the most common adverse events being headache (26%), fatigue (17%), diarrhea (14%), and nausea (13%). Alanine aminotransferase (ALT) elevation was reported in 5% of patients and led to discontinuation in 2 cases.

UNITY-II examined the same drug combination plus or minus RBV for 12 weeks in genotype 1 patients with compensated Child-Pugh class A cirrhosis.[3] SVR12 rates of 93% and 87% were seen in naïve and experienced patients, respectively, with DCV-TRIO alone. When RBV was included for G1a patients, SVR12 increased to 98% and 93%. The most commonly reported adverse events included headache (17%), nausea (14%), diarrhea (13%), and fatigue (12%). Fatigue and headache increased to 28% and 23%, respectively, when RBV was included. Three out of 202 patients discontinued therapy because of adverse events, 2 because of anemia and 1 because of anemia and increased aspartate aminotransferase (AST), all in the RBV group. DCV-TRIO has the opportunity to enter the competitive genotype 1 market in which more therapeutic options for physicians should only enhance patient care.

Daclatasvir/Sofosbuvir

The ALLY-3 trial combines daclatasvir (60 mg daily) with sofosbuvir (400 mg daily) for G3 patients in an open-label 12-week trial.[4] This regimen has previously demonstrated excellent efficacy in G1-3 with a 24-week duration.[5] Currently the only IFN-free therapy for G3 is sofosbuvir and RBV for a 24-week duration; this therapy has demonstrated higher rates of SVR (60%–94%) compared with 12- or 16-week durations.[6,7] Durations of 12 to 16 weeks in treatment-naïve patients had SVR rates of 55%, while treatment-experienced patients had SVR rates of 36% to 62%. IFN-ineligible patients treated for 12 weeks had overall SVR rates of 61%, 21% for cirrhotic patients and 68% for noncirrhotic patients. Treatment-experienced cirrhotic patients are not optimally served by this regimen, with SVR12 rates 19% to 60% with 12- to 16-week durations, respectively.[8] ALLY-3 examined SVR in treatment-naïve and -experienced cirrhotic and noncirrhotic patients. SVR rates of 97% and 94% were seen in noncirrhotic naïve and experienced patients, respectively. The presence of cirrhosis reduced SVR to 58% and 69%. The combination was well tolerated, with infrequent reported adverse effects of headache (20%), fatigue (18%), nausea (12%), and diarrhea (9%). No

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