What to do if standard therapy for hepatitis C fails

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Abstract

The standard of care for treatment of individuals chronically infected with hepatitis C virus is pegylated interferon in combination with ribavirin. Efficacy is closely related to viral genotype. This review outlines potential therapeutic strategies for treatment failures and discusses some of the newer agents currently in development.

Introduction and context

Hepatitis C virus (HCV) affects over 170 million people worldwide [1]. Infection itself is often asymptomatic but long-term can lead to the development of cirrhosis and hepatocellular carcinoma [2]. Since the molecular cloning of HCV in 1989, significant research into potential treatments for chronic HCV infection has been carried out [3]. The current standard of care is therapy with pegylated interferon (PEG-IFN α 2a or PEG-IFN α 2b) in combination with ribavirin for between 24 and 48 weeks. In genotype 2 and 3 infections, a sustained virological response (SVR), effectively a cure, can be achieved in 76-82% of individuals [4]. The SVR rates in the other genotypes are less favourable, especially the common genotype 1 infection in which SVR rates are less than 42-46% [5]. The question then arises of how to treat those patients who do not achieve an SVR despite full compliance with therapy. Potential strategies include dose optimisation, extended duration, additional treatments, and specifically targeted antiviral therapies for HCV (STAT-C).

Recent advances

Current work suggests that retreatment of individuals who have failed prior therapy may be beneficial in specific subgroups. A number of studies have shown that individuals who are relapsed responders (RRs) to IFN and ribavirin as opposed to non-responders (NRs) are more likely to respond to retreatment regimens, as are those who have received prior standard IFN rather

than PEG-IFN [6]. In these studies, the SVR rates for RRs treated with standard IFN and ribavirin were 42-45% as opposed to 8-17% for NRs and, in the EPIC (Efficacy of PEG-IFN in Chronic Hepatitis C) study, 36 versus 4% for RRs and NRs, respectively, when treated with PEG-IFN and ribavirin. Studies that have made combined analyses on individuals treated with IFN monotherapy or combination therapy have shown a pronounced effect of genotype on outcome, with SVR rates of 57-60% for genotype 2/3 as compared with 14-17% for genotype 1 [7,8]. Higher doses of ribavirin and IFN have been tested and look most promising for difficult-to-treat groups [9]. Weight-based dosing of ribavirin is important in individuals with genotype 1 infection treated with either PEG-IFN α 2a or PEG-IFN α 2b [10,11]. Increasing the dose of ribavirin from 13.3 to 15.2 μ g/kg per day (maximum dose of 1,600 mg ribavirin/day) can also improve SVR rates [12]. Prolonging the duration of therapy from 48 to 72 weeks may be beneficial in patients who are slow-responders (that is, remain PCR (polymerase chain reaction) positive at week 4) [13]. Initial data from the REPEAT (Retreatment with Pegasys in Patients Not Responding to Peg-Intron Therapy) study suggested that induction with high-dose PEG-IFN α 2a (360 μ g) may be beneficial in prior NRs, but it now appears that this enhanced benefit is more likely to be related to extending the duration of therapy [14]. Disappointingly, a trial of consensus IFN and ribavirin in PEG-IFN and ribavirin NRs gave SVR rates of only 6.9%

(9 µg consensus IFN) and 10.7% (15 µg) on intention-to-treat analysis [15].

STAT-C agents, given in combination with PEG-IFN and ribavirin, offer the greatest promise in the retreatment of prior NRs or relapsers to current optimal treatment regimens. However, viral resistance is common when they are given as monotherapy, hence the necessity of combination treatment. Two drugs, Telaprevir and Boceprevir, both NS3-NS4A protease inhibitors, have entered phase III testing. In phase II studies performed in combination regimens with PEG-IFN and ribavirin, Telaprevir achieved SVR rates of 61 and 67% [results from the Phase 2 Study of VX-950, Pegasys, and Copegus in Hepatitis C (PROVE)] and Boceprevir achieved an SVR rate of 57% [results from SPRINT (Serine Protease Inhibitor Therapy)] in IFN-naïve patients [16-18]. These agents induce a rapid decrease in HCV RNA, which in current PEG-IFN-based regimens is associated with SVR. PROVE 3 is currently studying Telaprevir in previously treated individuals, it also shows greater efficacy at the end of treatment in the relapsers to prior treatment as opposed to NRs [19]. Of note is that these agents can generate significant side effects, including fatigue, anaemia, and rashes (Telaprevir). Further studies of nucleoside polymerase inhibitors and non-nucleoside polymerase inhibitors are under way [20-23]. Whilst the emerging data on these new agents are exciting, viral resistance to them has been described as early as day 8. This has highlighted the need to avoid monotherapy and combine them either with drugs with nonoverlapping resistance profiles or with PEG-IFN and ribavirin [24,25].

Maintenance therapy

The concept of suppressing or halting disease progression using low-dose maintenance PEG-IFN has been evaluated in three long-term trials: CO-PILOT (Colchicine versus PegIntron Long-Term), EPIC, and HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis). Results from the HALT-C trial were published recently [26]. The rates of clinical outcomes and histological progression were, in general, similar between treated and untreated control groups, and therefore this strategy does not represent a viable treatment option for the majority of virologic NRs to current therapy.

Implications for clinical practice

Current studies are beginning to report successful retreatment with PEG-IFN and ribavirin in specific subgroups of individuals. Individuals who are RRs may benefit from retreatment with optimised dosages and durations of PEG-IFN and ribavirin. The key to successful treatment is to ensure adherence to the regimen, which

can be achieved with supportive nursing care. Induction with PEG-IFN or use of higher and weight-based dosing regimens of ribavirin may require additional haematological support with granulocyte-macrophage colony-stimulating factor and erythropoietin. However, true NRs are unlikely to gain benefit from a further course of PEG-IFN and ribavirin.

STAT-C agents in combination with PEG-IFN and ribavirin should become the mainstay of treatment for this group of individuals. However, the optimal dosage schedules for using them have yet to be determined. At present, Telaprevir and Boceprevir represent the most likely therapies to emerge on the market in the near future. Until then, inclusion in trial protocols may represent the best option for these individuals, with the caveat that there is a theoretical risk of selecting for resistant viral variants if these patients cannot be made to be rapid responders.

Abbreviations

CO-PILOT, Colchicine versus PegIntron Long-Term; EPIC, Efficacy of Pegylated Interferon in Chronic Hepatitis C; HALT-C, Hepatitis C Antiviral Long-term Treatment against Cirrhosis; HCV, hepatitis C virus; IFN, interferon; NR, non-responder; PCR, polymerase chain reaction; PEG-IFN, pegylated interferon; PROVE, Phase 2 Study of VX-950, Pegasys, and Copegus in Hepatitis C; REPEAT, Retreatment with Pegasys in Patients Not Responding to Peg-Intron Therapy; RR, relapsed responder; SPRINT, Serine Protease Inhibitor Therapy; STAT-C, specifically targeted antiviral therapy against hepatitis C; SVR, sustained virological response.

Competing interests

The authors declare that they have no competing interests.

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