Hepatitis C Therapy: Serendipitous Successes

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INTRODUCTION

Hepatitis C virus (HCV) infection is a growing epidemic worldwide, with about 170 million cases reported by 2011.[1] New therapies have been introduced to the market, but the prior mainstay of therapy involves pegylated interferon-alpha (IFN) along with ribavirin (RBV).[2] Treatment with the first generation direct-acting antiviral agent-containing regimens consisted of at least 24 weeks of therapy, with the goal of sustained viral response (SVR) – no detectable virus 24 weeks after treatment is completed. We report two cases in which therapy was terminated early due to the developed of severe infection, yet the patients still achieved SVR.

CASE REPORT

Case 1

A 54 year old woman with a benign meningioma, who had recently had the tumor resected, was found to have abnormal liver function tests. Subsequent testing revealed she had chronic HCV infection, genotype 3a, with a baseline viral load of $1.57x10^6$ IU/mL. There were no signs of chronic liver disease on exam, and an ultrasound of her abdomen revealed normal liver echogenicity without cirrhosis or hepatocellular carcinoma. 24 weeks of IFN and RBV was planned. After 4 weeks of treatment, she had no detectable virus (rapid virologic response). Although she tolerated the therapy, after 5 weeks of initiation, the patient developed a wound infection at the bifrontal craniotomy surgical site requiring a re-operation. The treatment was terminated and no further treatment plans were made with an IFN-based regimen. 24 weeks after early termination of treatment, at just 5 weeks, the patient had SVR and was feeling well.

Case 2

A 63 year old man with history of melanoma and thyroid goiter, presented for retreatment of genotype 1 HCV with cirrhosis after relapsing to a prior 48-week course of IFN and RBV, two years earlier. He was Child-Pugh class A and had no evidence of liver decompensation on examination. His baseline HCV RNA was $1.50x10^6$ IU/mL. He started treatment with IFN, RBV and telaprevir. He experienced side effects of therapy including anorectal burning, constipation, fatigue, and anemia requiring erythropoetin injections. He also achieved rapid virologic response at one month into therapy. Three months into therapy, the patient developed an abscess in the right axilla, which required surgical drainage and an indwelling drain. Antiviral therapy was terminated at that time. 64 weeks after termination of treatment, the patient remains in SVR with no complaints.

DISCUSSION

HCV infection is a leading cause of chronic liver disease worldwide.[3] While many patients with HCV may have a normal life expectancy, about 30% progress to end-stage liver disease, with the complications of cirrhosis and hepatocellular carcinoma.[1] Due to this threat of severe disease, much focus on developing effective therapies has occurred over the past ten years.[2] The mainstay of therapy has been IFN, which is used synergistically with RBV, likely through multiple mechanisms of action.[2] IFN is thought to inhibit HCV replication by inducing IFN-stimulated host genes that have antiviral functions. It also induces viral clearance, along with displaying biochemical and histological benefits.[4] This combination has been used in chronic HCV infection with rates of SVR estimated to be 31-67% depending on the HCV genotype, the dosage of IFN and RBV, and the duration of therapy[4]. Newer agents have recently been introduced, some of which act directly on viral targets, and others target host proteins essential to replication. The most commonly used agents from 2011-2013 were telaprevir and boceprevir, which are inhibitors of the N3/4A protease. A newer once daily protease inhibitor, simeprevir, and the first HCV polymerase inhibitor, sofosbuvir, are also now available in the US and more

than 15 agents are expected to be approved in the next four years. Future treatment looks to be IFN-free for most patients.

Response to HCV therapy has traditionally been monitored by measuring quantitative HCV RNA by a sensitive assay at weeks 4, 12, and 24 followed by 4 to 12 week intervals, at the end of treatment, and at 24 weeks after stopping treatment rather than by a clinical endpoint. The goal of therapy is to obtain SVR, which is defined as the absence of HCV RNA from serum at 24 weeks following discontinuation of therapy.[5] The achievement of SVR depends on HCV genotype, the interferon lambda 28B region in the host, and the early viral kinetics of treatment.[1] How quickly the virus is eliminated correlates with the rate of SVR [6], which is measured by rapid virologic response (RVR), defined as undetectable HCV RNA at week 4 of treatment. Patients who achieve an RVR may be able to shorten the duration of treatment but only 15-20% of persons with HCV genotype 1 infection and 66% with HCV genotype 2 and 3 infections achieve an RVR.[7] In our cases, both patients achieved RVR, predicting that their shorter courses may have been enough to achieve SVR.

While IFN and RBV have proven to be an effective combination in the treatment of HCV, they are associated with an often poorly tolerated side effect profile, leading to early termination of therapy in some patients. The most common adverse events include fatigue, headache, fevers, injection site reaction in greater than half of the patients, along with psychiatric side effects in 22-31% of patients.[5,8] Lab abnormalities are common, with neutropenia being a frequent indicator for IFN dose reduction or discontinuation.[1,5] Despite discontinuation of IFN being common in clinical practice for this reason, it has been shown that IFN-induced neutropenia does not necessarily predict the incidence of serious infection.[5,9] In our cases, IFN is likely implicated in increasing the patients' risk of infection

Typically early termination of therapy results in reduced efficacy of treatment, measured by rates of SVR. To achieve full efficacy, patients are expected to undergo greater than 80% of prescribed duration of treatment.[10] Patients who discontinued treatment prematurely had an SVR rate of 12% compared with 65% of those who continued treatment despite dose reduction.[11] Minimizing the duration of treatment has been investigated, due to the cost of therapy and side effect profile. In a study performed by Yu et al, it was found that SVR might be achieved for patients receiving a short treatment course of 8-16 weeks with IFN and RBV in genotype-2 patients with a RVR at week 4. It was also shown that a treatment duration of less than 20 weeks is likely inadequate for genotype-1 patients, before the advent of direct-acting antiviral agents.[4] It is unusual, as in our case, that SVR would be obtained in such a short treatment period. It raises the question as to whether concomitant severe infection while on IFN-based therapy may somehow enhance treatment success – a question that has not been thoroughly addressed in the literature to date. With the advent of new IFN-free therapies with shorter treatment durations and improved side effect profiles, including combinations of protease, NS5A, and polymerase inhibitors, with or without RBV, being evaluated and introduced to the market,[2] the study of early termination may not be relevant much longer, but remains an interesting medical curiosity.

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"Summer Love"
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