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Case Report

Induction with ribavirin in a relapsing patient with chronic HCV hepatitis

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ABSTRACT

In this case, a new possible strategy for treatment of hepatitis C virus (HCV) relapsing patients is described. The target of anti-HCV therapy is sustained viral response, but strategies for improving sustained viral response in relapsing patients would be useful, and ribavirin is crucial for obtaining viral response. Six weeks of induction therapy with ribavirin were used to improve efficacy of standard combined antiviral therapy in a patient relapsing to standard therapy. In the present case, the patient had undergone a retreatment with the same regimen with the exception of the six-week induction period with ribavirin. Use of induction therapy with ribavirin in this case has allowed for a sustained viral response without prolonging the interferon exposure time in retreatment.

Introduction

Hepatitis C virus (HCV) infection is an important cause of chronic liver disease that may lead to cirrhosis and hepatocellular carcinoma.[1,2] The primary goal of anti-HCV therapy is the permanent eradication of the virus, or a sustained viral response (SVR), which is equivalent to cure. Presently, the most effective treatment for chronic HCV infection is the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV). This combination antiviral therapy provides a SVR in approximately 50% of patients,[3] preventing HCV infection complications.[4,5] Although ribavirin's mechanism of action has not been fully elucidated, this nucleoside analogue has been shown to increase the antiviral effect of interferon (IFN) in HCV treatment in a dose-dependent manner.[6] Therefore, improving tolerability and adherence to the optimal dose of RBV in HCV infected patients is crucial to ensure high SVR rates. In addition, RBV pre-treatment has been tested in cases of chronic hepatitis C and shown to increase the efficacy of IFN.[7] Compliance during treatment and the dose of RBV are important factors for achieving SVR. Particularly, maintaining RBV dose is critical in patients with chronic hepatitis C who are treatment naive or who did not respond to a previous course of antiviral therapy.[8-10] Several data indicate that the dose of RBV is very important in preventing relapse.[8] A recent study demonstrated that patients treated with a weight-based RBV had a lower relapse rate than patients receiving fixed doses, especially in patients with high body weight.[11]

Despite this fundamental role of RBV, many aspects of the mechanism of action and of the optimal dose and duration of therapy remain to be defined. Some potential off-label use of this drug in more difficult-to-treat subjects has been proposed.[12] A case of induction with RBV for six weeks before retreatment of a HCV infected relapsing patient is described below.

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Case presentation

A 61 year-old white female was casually detected with HCV infection in 2006 by physician screening. The patient showed aspartate aminotransferases (AST) and alanine aminotransferases (ALT) serum levels within the normal range or slightly raised in the previous 12 months (< 2 normal range), WBC 6,700 cell/mmc and normal leukocyte formula, Hb 14.1 g/dL, PLT 218,000 cell/mmc, and HCV-RNA > 500,000 UI/mL, genotype 2a. She had hypertension under treatment with good control of blood pressure, body mass index (BMI) 34.2 kg/m^2, total cholesterol 224 mg/dL, HDL 65 mg/dL, triglycerides 163 mg/dL, AST 31 U/L, and ALT 32 U/L. It was decided to start treatment of HCV infection with PEG-IFNα2A 180 µg weekly plus RBV 1,200 mg/day (13.3 mg/kg/day) for 24 weeks. After one month of therapy, a rapid virological response was observed: transaminases were AST 30 U/L, ALT 36 U/L, and Hb dropped to 10.6 g/dL. Therapy was continued without changes and at the end of the treatment she presented a negative HCV-RNA, AST and ALT in normal ranges, and Hb 10.2 g/dL. Patient did not report missing any dose of RBV during control visits and the pill count confirmed this report.

However, one month after the end of antiviral therapy, she presented with HCV-RNA positive, AST 45 U/L, ALT 53 U/L, and Hb 12.2 g/dL. At the three months follow-up, the patient showed HCV-RNA > 500,000 UI/mL and Hb 14 g/dL.

Because the patient was strongly motivated to undergo a new treatment, retreatment with off-label use of RBV was chosen. A clinical control after six months showed HCV-RNA > 500,000 UI/ml, AST 41 U/L, ALT 53 U/L, Hb 13.7 g/dL, and BMI 34 kg/m^2. Therapy started with 13.3 mg/Kg/day of RBV alone for six weeks, followed by PEG-IFNα2A 180 µg weekly plus RBV 13.3 mg/Kg/day for 24 weeks. After six weeks of RBV alone, before starting combined therapy with PEG-IFN plus RBV, the patient had HCV-RNA 125,000 UI/mL, ALT 36 U/L, AST 38 U/L, Hb 10.7 g/dL, total cholesterol 211 mg/dL, HDL 83 mg/dL, triglycerides 91 mg/dL. After one month of combined antiviral therapy, negative HCV-RNA, transaminases in the normal range, and Hb 10.4 mg/dL were observed. At the end of treatment, HCV-RNA was negative, Hb 9.5 g/dL, and AST and ALT were in normal range. Epoietin was neither used in the first nor in the second treatment course.

Six months after the end of anti-HCV therapy, the patient had normal aminotransferases serum levels and a sustained viral response.

Discussion

In this case a new possible strategy for treating relapsing patients is described. Six-week induction therapy with RBV was used to improve efficacy of the standard combined antiviral therapy. RBV is a direct antiviral agent but has also been shown to modulate immune response. RBV inhibits inosine 5' monophospate dehydrogenase, which is responsible for the intracellular synthesis of guanine, and consequentially reduces RNA viral replication.[13] Furthermore, a recent study suggests that RBV potentiates the anti-HCV effect of IFN, augmenting the induction of interferon-stimulated genes in patients treated for HCV infection.[14] Merli et al. indicate that RBV pre-treatment increased the tolerability of the antiviral therapy, and improved its efficacy in liver transplant patients.[15]

In this patient, the six-week induction therapy with RBV produced a slight decline of HCV-RNA plasma level, and it may be hypothesized that this strategy enhanced viral clearance during combination therapy. Use of induction therapy with RBV in this case seemed to assure a good adherence to combination treatment, probably because it makes the side-effects of the two drugs asynchronous, which might improve patient's compliance. On the basis of RBV pharmacokinetics, a six-week RBV pre-treatment could optimize the preparation of the hepatic cell machinery to IFN activity. In this patient RBV monotherapy was capable of significantly reducing HCV-RNA levels, in accordance with the literature.[16,17]

A particularity in the present case is that the patient had undergone retreatment with the same regimen, with the exception of induction for six weeks with RBV. Currently, relapsing patients are treated for a longer period with combination therapy to improve the success rate, because it is known that patients retreated with the same regimen, even if the type of interferon is changed, have a very low response rate.[18]

RBV pre-treatment improved efficacy in this HCV relapsing patient. Moreover, HCV-RNA decline during pre-treatment with RBV allows one to make an useful prediction about treatment results. In the present case the patient had undergone a re-treatment with the same regimen with the exception of induction with six weeks of RBV. In conclusion, if further studies should confirm this observation, there would be a reduction of the combination therapy time, of these patients' management costs, and of drug-induced adverse events. Randomized trials are needed to confirm the effectiveness of this RBV induction therapy strategy, which may be an important new method to achieve SVR in HCV-infected relapsing patients.

Conflict of interest

All authors declare to have no conflict of interest.

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