

Ribavirin Desensitization in Chronic Hepatitis C

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Infection with hepatitis C virus (HCV) affects an estimated 185 million people globally, with up to 30% of chronically infected individuals developing cirrhosis within two to three decades. According to the latest practice guidelines issued by the American Association for the Study of Liver Diseases, the treatment of genotype 1 chronic HCV infection still includes ribavirin and to a lesser extent, PEG-interferon (IFN), together with a combination of new oral anti-HCV direct-acting antivirals [1]. Dermatological adverse effects of Peg-IFN plus ribavirin combined therapy account for > 10% of all interferon-associated side effects. Common dermatological adverse reactions include generalized pruritus, and eczematiform lesions on extremities and truncal sites exposed to friction. In the era of the new direct-acting antiviral drugs, dermatological adverse reactions to ribavirin may even increase. When a hypersensitivity reaction to a drug occurs and there is no alternative treatment, the only therapeutic option is to perform a desensitization procedure [2]. We present here a case of successful desensitization to ribavirin in a patient with chronic HCV infection.

PATIENT DESCRIPTION

A 57 year old female patient with chronic HCV infection genotype 1a, cirrhosis, mild

asthma and allergic rhinitis had previously been treated with interferon (Pegintron[®], Merck, USA) and ribavirin (Rebetrol[®], Merck, USA). Therapy was discontinued after the patient developed a generalized maculopapular rash and severe pruritus. Two days after beginning a second attempt of therapy with different brands of ribavirin (Copegus[®], Hoffmann-La Roche, Inc. c/o Genentech, Inc. USA) and interferon (Pegasys[®], Hoffmann-La Roche, Inc. c/o Genentech, Inc. USA) the patient presented with shortness of breath and diffuse urticaria necessitating the use of systemic corticosteroids and antihistamines and treatment cessation. Following recovery, a single dose of interferon was administered with no adverse effects. A ribavirin desensitization protocol was initiated with 50 µg ribavirin, doubling the dose every 3 days to a one tablet (200 mg) dose over a period of 1 month [Table 1], thereby gradu-

ally increasing to the target daily dose of 1000 mg. The desensitization procedure was well tolerated, and when completed, interferon was added successfully. Therapy was prematurely discontinued at week 32, following two episodes of febrile neutropenia. Nevertheless, the patient achieved a sustained virologic response at week 12 and her polymerase chain reaction (PCR) was negative 6 months later. At the last clinical follow-up, 3 years following the desensitization, there was no evidence of recurrence.

COMMENT

A Cochrane Database meta-analysis comparing the combined therapy of ribavirin and interferon versus Peg-IFN monotherapy found that the combined therapy further increases the risk of cutaneous reactions [3]. The response rate and 95% confidence interval (CI) was 1.67 (95%CI 1.21–2.30) for dermatitis, 1.62 (95%CI 1.29–2.02) for pruritus, and 1.74 (95%CI 1.17–2.6) for rash. In a recent study of 286 chronic HCV patients treated with IFN-alpha formulations plus ribavirin, dermatologic eruptions were a contributing factor in the decision to discontinue antiviral treatment in 10% of cases, emphasizing the importance of applying desensitization protocols for these patients [4]. Our patient developed a delayed-type hypersensitivity reaction to ribavirin.

By slowly increasing the dose of ribavirin to therapeutic dosage, she was successfully desensitized and was able to resume treatment with the drug. Delayed-type hypersensitivity reactions to drugs involve T cell activation (Gell and Coombs type IVa-d reactions) that interact with activated keratinocytes and initiate the inflammatory skin reaction. Viral infections (e.g., HCV

Table 1. Ribavirin desensitization protocol

Interval (day)	Solution	Volume (ml)	Daily dose (mg)
1-3	2	0.25	0.05
4-6	2	0.5	0.1
7-9	2	1	0.2
10-12	2	2	0.4
13-15	2	5	1
16-18	1	2.5	5
19-21	1	5	10
22-24	1	10	20
25-27	1	25	50
28-30	½ tablet	–	100
31	One tablet	–	200

Solution 1: Suspension was prepared by crushing 2 tablets (200 mg x 2 = 400 mg) of ribavirin into a volume of 200 ml diluent (2 mg/ml)

Solution 2: 1:10 dilution of solution 1, final concentration 0.2 mg/ml

*The first two authors contributed equally to this study

infection) may stimulate expression and presentation of processed drug antigens on MHC molecules to drug-specific T cells, which lowers their activation threshold for a delayed skin reaction. The first step when evaluating a hypersensitivity reaction to a drug is to exclude other non-allergic causes and then identify the culprit drug. Hence, one should differentiate between an immediate-type IgE reaction (urticaria, angioedema or systemic reactions, occurring within 1 hour) and a delayed-type hypersensitivity reaction (usually a maculopapular rash).

Drug desensitization should be considered when there is no other therapeutic alternative and the benefits of the procedure outweigh the risks. This procedure leads only to a temporary state of tolerance, and if the drug is discontinued the tolerance state is lost. Drug desensitization is defined as the induction of a temporary state of tolerance to a drug responsible for a hypersensitivity reaction. It is performed by administering increasing doses of the medication until

the total cumulative therapeutic dose is achieved and tolerated. Contraindication of desensitization includes severe life-threatening drug-induced cutaneous reactions such as Steven-Johnson syndrome/toxic epidermal necrolysis or a systemic reaction (e.g., vasculitis, autoimmune disorders or internal organ involvement) [5]. In desensitization of delayed-type hypersensitivity reactions, tolerance is usually achieved within days to several weeks and the procedure can be performed in an ambulatory setting. Desensitization protocols for delayed-type reactions have been applied with several drugs, with high rates of success. There is no consensus on drug desensitization protocols for hypersensitivity reactions, and the initial dose may vary from 1:8 to 1:10⁶ of the therapeutic daily dose [5].

In conclusion, ribavirin desensitization in chronic HCV patients developing skin eruptions can be implemented safely and successfully. This procedure expands the therapeutic solutions for treating chronic HCV patients and may be implemented

with other drugs to help increase treatment completion rates.

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