

Skin Rash During Chronic Hepatitis C Therapy

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Hepatitis C virus (HCV) infection remains a significant clinical and public health challenge, with approximately 4.1 million individuals infected in the United States.¹ The World Health Organization estimates that 3–4 million individuals are infected each year worldwide, with a global 170 million chronic HCV carriers at risk of developing liver cirrhosis and/or liver cancer. Various types of skin rash have been reported due to HCV infection, as well as anti-HCV treatment. Some skin rashes improve with anti-HCV treatment, whereas others worsen, necessitating the discontinuation of the treatment and the initiation of therapy targeted toward the rash itself. We describe 3 cases that illustrate the therapeutic dilemmas that can arise when a patient develops a skin rash during treatment with pegylated interferon alfa-2a with ribavirin.

Case Series

Case #1

A 47-year-old Hispanic woman presented with a 2-day history of inflammatory skin lesions on her arms and legs. Her medical history was remarkable only for HCV infection, and she was on Week 1 of therapy with pegylated interferon alfa-2a (180 µg once a week) and ribavirin (1,200 mg daily). The patient developed pruritic, confluent, papular erythematous eruptions with occasional vesicles over her arms and legs away from the peginterferon injection site (Figures 1 and 2). She had no history of dermatologic disease or atopy.

The patient had genotype 1 HCV infection, with a viral load of 1,240,000 IU/mL prior to the initiation of anti-HCV therapy. Laboratory examination at the time of the development of the skin rash showed a decrease in white blood cell count (3,200/µL), red blood cell count (442×10^6 µL), hemoglobin (14 g/dL), and platelets (49,000/µL), as well as elevations in aspartate aminotransferase (70 IU/L) and alanine aminotransferase levels (44 IU/L).

Due to severe discomfort from the rash, ribavirin was discontinued with the intention to resume therapy



Figure 1. Confluent erythematous rash on the lower extremity of the patient described in case #1.

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Figure 2. Erythematous rash with vesicles on the upper arm of the patient described in case #1.



Figure 3. Resolution of the rash shown in Figure 1 after discontinuation of ribavirin.



Figure 4. Resolution of the rash shown in Figure 2 after discontinuation of ribavirin.

once the rash resolved. By Day 4, the patient reported significant improvement of the skin lesions, and ribavirin therapy (1,200 mg daily) was resumed. The patient tolerated the therapy without reappearance of the rash (Figures 3 and 4).

Case #2

A 43-year-old white woman presented with a 4-day history of inflammatory skin lesions on her face, neck, arms, and legs. Her medical history was remarkable only for HCV infection, and she was on Week 3 of therapy with pegylated interferon alfa-2a (180 µg once a week) and ribavirin (1,200 mg daily). The eruptions were limited to the pegylated interferon alfa-2a injection sites after the initial 2 treatments. However, after Week 3, the patient developed pruritic, confluent, papular erythematous eruptions with occasional vesicles on her face, neck, arms, and legs away from the injection sites.

The patient had genotype 1 HCV infection, with a viral load of 1,500,000 IU/mL prior to the initiation of anti-HCV therapy. Laboratory examination at the time of the development of the skin rash showed a decrease in white blood cell count (1,700/µL), red blood cell count (370×10^6 µL), hemoglobin (12 g/dL), and platelets (76,000/µL), as well as elevations in aspartate aminotransferase (61 IU/L) and alanine aminotransferase levels (38 IU/L).

We recommended the use of moisturizing lotion and steroid topical cream (1% hydrocortisone) to the affected areas and continued anti-HCV therapy. The patient reported mild improvement in the skin lesions. We subsequently started the patient on oral antihistamine (diphenhydramine 25 mg every 6 hours), which relieved her symptoms at the time. However, at Week 8 of anti-HCV therapy, she noticed the worsening of her skin lesions and pruritis.

Due to the severity of the rash, ribavirin was discontinued with the intention to resume therapy once the rash was reasonably controlled. By Day 5, the patient reported significant improvement of the skin lesions, and we recommended the resumption of ribavirin. The patient tolerated the therapy without reappearance of the rash.

Case #3

A 51-year-old woman presented with a 2-day history of inflammatory skin lesions on her arms and legs. Her medical history was remarkable only for HCV infection, and she was on Week 2 of therapy with pegylated interferon alfa-2a (180 µg once a week) and ribavirin (1,200 mg daily). The first week of anti-HCV therapy was uneventful, but the patient subsequently developed pruritic, confluent, papular erythematous eruptions with occasional vesicles over her abdomen, arms, and legs away from the injection sites.

The patient had genotype 1 HCV infection, with a viral load of 239,000 IU/mL prior to the initiation of anti-HCV therapy. Laboratory examination at the time of the development of the skin rash showed a decrease in white blood cell count (2,300/µL), red blood cell count

(465×10^6 μL), hemoglobin (14.4 g/dL), and platelets (71,000/ μL), as well as elevations in aspartate aminotransferase (175 IU/L) and alanine aminotransferase levels (190 IU/L).

Due to severe discomfort from the rash, ribavirin was discontinued. By Day 4, the patient reported significant improvement of the skin lesions, and we recommended the resumption of ribavirin. The patient tolerated the therapy without reappearance of the rash.

Discussion

Various types of dermatologic manifestations have been reported due to HCV infection and during anti-HCV therapy. The incidence of skin lesions during anti-HCV therapy is 24–28%, according to randomized controlled clinical trials.^{2–4} Fried⁵ reported that injection-site reactions occurred in approximately 60% of cases. In the cases discussed above, skin lesions developed away from interferon injection sites. Interestingly, the rash improved with the discontinuation of ribavirin for several days, and none of the patients experienced a recurrence of the rash after rechallenging the ribavirin therapy.

The exact mechanism of ribavirin-induced skin rash during the early stage of anti-HCV therapy is unknown. Skin reactions that occur during the early course of anti-HCV therapy may be due to histamine-like side effects from ribavirin. Ribavirin has been found to cause itching, nasal stuffiness, recurrent bronchitis, and asthma-like symptoms. These histamine-like side effects occur in 10–20% of patients and are usually mild to moderate in severity. Stryjek-Kaminska and colleagues⁶ have reported photoallergic skin reactions from ribavirin. However, in our case series, some of the patients developed skin lesions in areas not exposed to the sun, and none of the patients experienced a recurrence of lesions after reintroducing ribavirin.

Skin lesions may vary in severity from localized rash to diffuse skin involvement. Depending upon the severity of the rash, we recommend topical therapies, starting with moisturizing lotions or steroid skin cream (eg, 1% hydrocortisone or triamcinolone). Oral antihistamines may be helpful if topical therapies do not relieve symptoms. If skin lesions worsen despite the measures discussed above, we recommend discontinuing ribavirin until the rash resolves and then reintroducing ribavirin.

The development of diffuse skin lesions during the early course of anti-HCV therapy has been reported in Europe^{7,8} and Asia⁹ but not in the United States to our knowledge. This paper may be the first reported case series

in the United States. We think that these skin lesions are common in early anti-HCV therapy and are underreported in the United States. In their case series, Dereure and colleagues⁷ found nonspecific skin biopsies with a dermal, mainly perivascular, mononuclear infiltrate. They also noted that skin testing was poorly informative and not predictive of relapse. In all previously reported cases from other continents, it was unclear whether interferon or ribavirin was the contributing factor for the rash. In our case series, it is clear that discontinuing ribavirin for several days (less than a week) was sufficient to recover from the rash, and none of our patients required discontinuing pegylated interferon alfa-2a.

Summary

Our 3 cases show that skin rash during early anti-HCV treatment away from interferon injection sites is due to ribavirin. Depending upon the severity of the rash, we recommend topical therapies, starting with moisturizing lotions or steroid skin cream (eg, 1% hydrocortisone or triamcinolone). Oral antihistamines may be helpful if topical therapies do not relieve symptoms. If skin lesions worsen despite the measures discussed above, we recommend discontinuing ribavirin until the rash resolves and then reintroducing the drug. Skin testing and histology are often not initially necessary.

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Review

Hepatitis C Virus Therapy–related Skin Manifestations

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Hepatitis C virus (HCV) infection is a significant global health problem. The World Health Organization estimates that approximately 130–170 million individuals worldwide and 1–2.5% of the US population are chronically infected with HCV.¹ Patients with HCV are at risk for significant complications such as the development of cirrhosis and hepatocellular carcinoma (HCC). Due to the high prevalence of HCV liver disease, HCV is the leading indication for liver transplantation worldwide.

Because of the high morbidity and mortality associated with HCV infection, attempts should be made to eradicate the virus. Standard treatment of HCV consists of combined pegylated interferon (either alfa-2a or -2b) and ribavirin, with the primary goal of achieving sustained virologic response (SVR). SVR reduces the risk of HCV-infected patients developing fibrosis and progressing to cirrhosis, lowers the risk of HCC, and improves overall liver-related mortality and morbidity.^{2–6}

SVR rates range from 20% to 80%, depending upon factors such as HCV genotype, baseline viral load, presence of advanced fibrosis, insulin resistance, and ethnicity.^{2–6} SVR is also influenced by the length of treatment (usually 48 weeks for genotypes 1 and 4, and 24 weeks for genotypes 2 and 3),⁷ dosing,^{8,9} and patient compliance. McHutchison and associates¹⁰ demonstrated that SVR is significantly impacted by adherence to therapy. HCV genotype 1 patients who received at least 80% of their pegylated interferon and ribavirin for at least 80% of the expected duration of therapy experienced a significant difference in SVR compared to those with less than 80% of dosing (63% vs 34%; $P=.008$). Therefore, treatment adherence at the recommended therapeutic dosages is essential in order to achieve SVR.

However, pegylated interferon and ribavirin are associated with many side effects that can impact patient

compliance, dosing, and subsequent SVR. Pegylated interferon is associated with myalgias, arthralgias, fever, fatigue, nausea, diarrhea, headaches, neutropenia, depression, and rash. Ribavirin is associated with hemolytic anemia, nausea, insomnia, and rash. Veluru and colleagues¹¹ describe 3 patients with chronic HCV infection who developed what were likely ribavirin-related skin eruptions during antiviral treatment. All 3 patients developed severe inflammatory skin lesions, which were occasionally pruritic, and all required ribavirin cessation. After a brief drug holiday, the skin manifestations of all 3 patients resolved, and antiviral therapy was restarted.

Because both HCV infection and therapy are associated with cutaneous manifestations, it may be difficult to differentiate between HCV-related and therapy-related skin changes. Up to 38% of HCV-infected patients experience extrahepatic manifestations,¹² and up to 17% are dermatologic.¹³ These conditions include prurigo nodules, purpura secondary to mixed cryoglobulinemia, porphyria cutanea tarda, and lichen planus. Most dermatologic findings related to HCV infection are treated with antiviral therapy, along with supplemental topical treatments.¹⁴

Adverse cutaneous reactions are common but are typically treatable complications of HCV combination therapy. Physicians should be aware of these findings and prepared to treat them. Cutaneous side effects associated with interferon and ribavirin treatment are heterogeneous and typically mild, though severe reactions can occur on very rare occasions. Interferon has an overall incidence of cutaneous eruptions of 13–23%.¹⁵ The cutaneous side-effect profile of interferon includes transient alopecia, vasculitis, cutaneous necrosis, lichen planus, psoriasis,^{16,17} and, most commonly, injection-site reaction, which is seen in up to 60% of patients.¹⁸ Severe skin reactions (including vesiculobullous eruptions, erythema multiforme, and generalized exfoliative dermatitis or erythroderma) have rarely been reported in patients treated with peginterferon alfa-2a alone or in combination with ribavirin.^{19,20} Stevens-Johnson syndrome and toxic epidermal necrolysis have not been reported.²⁰ Oral ribavirin in combination with peginterferon alfa-2a, peginterferon alfa-2b, or interferon alfa-2b has been associated with alopecia, pruritus, dermatitis (in over 20% of patients), dry skin, increased sweating, and generalized morbilliform rash. The majority of HCV treatment-associated rashes are thought to be caused by ribavirin based upon the sharp increase in incidence when ribavirin was introduced to the interferon-based regimens.²¹ On the other hand, the substitution of interferon with its pegylated form did not lead to an increased incidence of adverse skin effects.⁹

Morbilliform eruptions are generally the most common adverse drug reactions. These rashes tend to be fine, red, petechial, reticular, and most commonly seen on the

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arms and trunk, though they can be seen diffusely in more severe cases. The lesions start as erythematous macules that can become palpable in a symmetric distribution, typically starting on the trunk and spreading to the extremities. Mucous membranes are generally spared. Classically, in morbilliform eruptions, the underlying mechanism is thought to be immunologic and is considered a cell-mediated type IV hypersensitivity reaction, though the mechanism is likely more complex and varies depending upon the offending drug. The exact pathophysiology of drug eruptions associated with ribavirin has yet to be elucidated. The cutaneous reaction typically begins 7–14 days after a drug has been started but can be seen later.²² Patients treated with combination HCV therapy become more reactive to allergens while on therapy, and enhancement of a T-helper-1-type profile has been seen.²³ It has been suggested that histamines may be closely associated with the rash due to ribavirin, but additional studies are necessary to confirm this hypothesis.

Initial evaluation of a patient with a cutaneous side effect from HCV treatment should include a full skin examination in order to exclude rare but serious or life-threatening reactions. Clinical features suggestive of a serious reaction include edema of the face, peripheral hypereosinophilia, blistering, mucous membrane lesions, and intensely painful or dusky skin lesions. Treatment should provide patient comfort and symptom control. Topical application of class III corticosteroids (ie, clobetasone butyrate or triamcinolone acetonide cream or ointment) is generally sufficient for topical therapy. Weaker topical steroids (ie, hydrocortisone) may provide relief in mild cases. Systemic steroids should be avoided due to the risk of altering hepatitis C viral loads.²⁴ Patients should be instructed to apply daily baseline thick emollients and to avoid harsh soaps and any other irritating topical therapies. Treatment with oral antihistamines for symptomatic relief from itching can be added. Reasonable regimens include a morning low-sedation or second-generation H₁ antihistamine (ie, loratadine, cetirizine, or fexofenadine) and an evening first-generation H₁ antihistamine (ie, hydroxyzine or diphenhydramine hydrochloride).

Most patients with HCV treatment-associated drug reactions may continue their combination therapy without interruption, if appropriate skin treatment is instituted. Treating through (ie, continuing the drug despite a cutaneous eruption in the case of a ribavirin-induced rash) can consist of decreasing the dose of ribavirin, temporarily discontinuing the treatment, or continuing the therapy at full dose and symptomatically controlling the disease. Although there is a paucity of controlled studies to determine the utility of decreasing the dose or stopping ribavirin due to cutaneous side effects, in

general, most patients with drug eruptions will see the eruptions disappear even though the drug is continued at full dose. The plasma half-life of ribavirin is 30–40 hours after just 1 dose, whereas at steady state, the half-life is 200–300 hours.²⁵ Therefore, stopping the drug for very short periods of time provides only a small decrease in plasma concentration of the medication. When comparing randomized controlled studies in different HCV treatment regimens, a lower ribavirin dose had a minimal effect on the incidence of rash as an adverse event. In a study of 511 patients treated with peginterferon alfa-2b and ribavirin 800 mg daily, 24% experienced rash associated with treatment.²⁶ Another study found that among patients treated with peginterferon alfa-2b weekly and ribavirin 1,000–1,200 mg daily (228 patients), 28% experienced dermatitis or rash associated with treatment.²¹ Some morbilliform lesions and early erythema multiforme lesions have similar appearances and can be easily confused; therefore, cutaneous lesions should be monitored if therapy is to be continued to ensure that these lesions do not become more serious.

HCV infection remains an important global burden, and treatment clearly demonstrates a benefit in liver-related morbidity and mortality. It is crucial to emphasize that treatment with pegylated interferon and ribavirin should be continued for the entire duration, as much as can be tolerated. Significant dose reductions (>20% of the targeted dose),^{7,10} as well as prolonged discontinuation, can lead to significantly lower SVR rates (53% vs 68%; $P=.004$) and higher relapse rates after treatment (42% vs 29%; $P=.02$).⁸ Other trials have also stressed the importance of the continuation of both drugs without interruptions in order to maximize the chance of achieving SVR.^{8,10,27} Combination therapy remains the standard of care for HCV treatment, and ribavirin continuation at maximal dosing does appear to provide a greater chance of achieving early/rapid viral response and preventing relapse.¹⁰

Although the mechanism of ribavirin is not completely understood, it is known that ribavirin provides moderate antiviral effects that can sustain SVR at a higher rate than interferons alone.^{21,28} Proposed mechanisms of action include depleting guanosine triphosphate levels through inhibition of the enzyme inosine monophosphate dehydrogenase, as well as hindering the HCV RNA-dependent polymerase.^{8,29} Viral kinetics from ribavirin have been investigated, and it has been demonstrated that viral inhibition is immediate during the first several days of administration, though it can be quickly reversible.³⁰ Studies have also revealed that ribavirin can also enhance the clearance of infected cells and play a key role in the prevention of later-phase HCV replication, which is thought to be the reasoning for post-treatment

relapses.³¹ In addition, immunomodulating effects have been studied, revealing a ribavirin-induced activation of T-helper response among T-helper 1 cells, thus increasing intracellular response toward infected cell clearance.³²

Given ribavirin's biological and clinical importance in maintaining antiviral activity, treatment with ribavirin should ideally continue throughout the entire duration of HCV treatment at therapeutic doses. Physicians should be familiar with the rashes associated with HCV treatment and their management, as well as the importance of minimizing HCV treatment interruption. In doing so, SVR rates are maximized, leading to a reduction in liver-related morbidity and mortality.

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