Case Report/Case Series

Widespread Morbilliform Eruption Associated With Telaprevir Use of Dermatologic Consultation to Increase Tolerability

Lauren Strazzula, BA; Daniel S. Pratt, MD; Janet Zardas, NP; Raymond T. Chung, MD; Michael Thiim, MD; Daniela Kroshinsky, MD, MPH

Importance Telaprevir, combined with pegylated interferon alfa and ribavirin, is an efficacious approach to treat hepatitis C virus infection. A morbilliform eruption associated with telaprevir is a common adverse effect experienced by patients. Current guidelines mandate telaprevir discontinuation in any patient with a severe, progressive, or unresponsive cutaneous eruption.

Observations Eight patients with a grade 3 (severe) widespread morbilliform eruption associated with telaprevir were referred to dermatology for evaluation and treatment. Each patient received a combination of antihistamines, topical corticosteroids, and thick emollient creams, rendering their eruption tolerable for the duration of treatment. No patients had evidence of a systemic or life-threatening drug reaction, developed a systemic drug eruption, or had to prematurely stop triple therapy secondary to a cutaneous eruption.

Conclusions and Relevance Patients with an uncomplicated grade 3 (severe) widespread morbilliform eruption associated with telaprevir may be able to continue triple therapy with close monitoring and dermatologic consultation. Given our findings, we propose an additional clinical classification of the telaprevir-associated eruption to better reflect the dermatologic classification of drug eruptions.

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Hepatitis C virus (HCV), the leading cause of liver transplantation in the United States, is associated with significant morbidity and mortality worldwide.1 In 2011, telaprevir, a HCV serine protease inhibitor, was approved by the US Food and Drug Administration to treat chronic HCV infection in combination with ribavirin and pegylated interferon alfa.2 This triple combination therapy has greatly improved the prognosis of individuals infected with HCV and is an efficacious treatment for this traditionally drug-resistant disease. However, the use of triple therapy has been limited in a subset of patients because of adverse effects. In phase II and III randomized clinical trials of telaprevir, medication-related cutaneous eruption occurred in approximately 56% of patients receiving at least 1 dose of telaprevir, and telaprevir was discontinued in 6% of patients because of adverse dermatologic events.3-7

In efforts to improve the evaluation and management of a telaprevir eruption and to prevent unnecessary treatment discontinuation, a schema was created during clinical trials to grade the severity of the eruption, whereby grade 1 (mild) is a localized eruption and/or pruritus, grade 2 (moderate) is a diffuse eruption affecting 50% or less of total body surface area (TBSA), and grade 3 (severe) involves more than 50% of TBSA, has atypical features such as epidermal detachment or bullae, or is associated with systemic signs or symptoms.3-6 According to these guidelines, uncomplicated grade 1 and 2 telaprevir eruptions, which comprise more than 90% of total reported eruptions, can be treated symptomatically, with no need to discontinue therapy.3-6,8 However, these guidelines mandate telaprevir be discontinued if a patient has a grade 3 or a progressive or treatment-resistant grade 2 eruption.3-6 If the eruption does not resolve with telaprevir discontinuation, ribavirin and pegylated interferon alfa are subsequently stopped.3-6,8

Recently, reports of fatal telaprevir-associated systemic drug reactions, such as drug rash with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), led to the issuance of a boxed warning by the US Food and Drug Administration.9 These reported severe events underscore the importance of hepatologists monitoring the safety of patients with a telaprevir eruption and suggest a need for better guidelines to evaluate and manage telaprevir-associated cutaneous eruptions. At the same time, many patients receiving this therapy have failed all other existing treatment options, resulting in great motivation to attempt to complete a full course of therapy if possible.

Report of Cases

Eight patients with chronic HCV being treated with telaprevir, ribavirin, and pegylated interferon alfa who had a wide-
spread morbilliform eruption associated with telaprevir were referred to dermatology (Table 1). Each patient had an eruption that affected more than 50% of his or her TBSA and was subsequently categorized as having a grade 3 telaprevir eruption (Figure). Institutional review board approval and informed consent were not needed since this study was performed during routine clinical care.

Seven men and 1 woman, with a mean age of 60.4 years, developed a morbilliform eruption a mean of 20.1 days following treatment initiation. The patients were evaluated a mean of 13.3 days following the reported onset of symptoms. The eruption was universally described as morbilliform papules and plaques, many of which had an erythematous to violaceous hue. The trunk and extremities were affected in all patients, while facial and genital involvement was less common. Upon presentation, none of the patients had eosinophilia or liver function test results above baseline that would indicate systemic involvement. A punch biopsy was performed on 1 patient that showed a spongiotic dermatitis with focal parakeratosis, scattered dyskeratosis, a superficial perivascular lymphocytic infiltrate with plasma cells, and erythrocyte extravasation consistent with drug hypersensitivity.

The eruption lasted a mean of 54.9 days, and 4 patients were affected until the course of telaprevir was completed. Each patient was treated with topical corticosteroids, thick emollients, and antihistamines. No patients had to discontinue therapy secondary to the widespread eruption. Telaprevir was prematurely stopped in 1 patient at week 8 because of severe fatigue and anemia unrelated to his rash. Two patients did not receive a full course of treatment with ribavirin and/or pegylated interferon alfa therapy due to thrombocytopenia and shoulder pain. One patient had a viral breakthrough and discontinued ribavirin and pegylated interferon alfa per protocol. No patients had progression to a systemic or more serious drug eruption such as DRESS or SJS/TEN. Six patients have sustained viral responses, and their disease is in remission.

**Discussion**

The mechanism of telaprevir-associated cutaneous eruptions remains largely unknown. A recent study suggested that telaprevir eruptions may be a form of eczematous dermatitis, but this would not fully explain the ability of these reactions to coalesce into widespread eruptions.

### Table 1. Characteristics of 8 Patients Treated for Grade 3 (Severe) Telaprevir Eruption

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient No.</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>1 2 3 4 5 6 7 8</td>
</tr>
<tr>
<td>Male</td>
<td>Male</td>
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<tr>
<td>Male</td>
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<td>Male</td>
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<td>Male</td>
<td>Female</td>
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<tr>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Treatment naïve</td>
<td>– + – – – – – –</td>
</tr>
<tr>
<td>History of eruption with ribavirin or peglated interferon alfa</td>
<td>– – + – + – – –</td>
</tr>
<tr>
<td>Eruption onset after treatment initiation, d</td>
<td>32 22 3 47 3 4 28 22</td>
</tr>
<tr>
<td>Seen by dermatology, days after rash began</td>
<td>7 14 12 14 0 0 37 22</td>
</tr>
<tr>
<td>Able to complete telaprevir? (if not, weeks completed)</td>
<td>+ + + + + – (8) + +</td>
</tr>
<tr>
<td>Able to complete all therapy? (if not, weeks completed)</td>
<td>+ - (43) + - (13) + + - (12) IP</td>
</tr>
<tr>
<td>Rash resolution, d</td>
<td>32 151 76 46 6 7 61 60</td>
</tr>
<tr>
<td>Seen by dermatology, No. of visits</td>
<td>1 1 1 1 5 2 1 1</td>
</tr>
<tr>
<td>Current viral load, HCV RNA PCR, IU/mL</td>
<td>ND ND 694000 ND ND ND 510000 ND</td>
</tr>
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Abbreviations: HCV, hepatitis C virus; IP, in progress, patient currently completing therapy; ND, not detected; PCR, polymerase chain reaction; +, completed; -, did not complete.

* All treatment failure due to noncutaneous adverse effects.
to progress to DRESS or SJS/TEN. In our experience, patients with a grade 3 telaprevir eruption have all had a morbilliform eruption, and a biopsy obtained from 1 patient showed histopathologic findings characteristic of cutaneous drug hypersensitivity. Interestingly, 2 of our patients had 2 concomitant morphologically distinct eruptions, a diffuse morbilliform eruption characteristic of a grade 3 telaprevir eruption, and a localized eczematous eruption around pegylated interferon alfa injection sites.

Despite the lack of understanding the pathogenesis of telaprevir eruptions, this series demonstrates that the signs and symptoms can be managed similarly to other cutaneous drug eruptions. Patients can be “treated through” the duration of triple therapy with an aggressive and comprehensive treatment regimen, including mid- to high-potency topical corticosteroids, thick emollient creams, and antihistamines. Seeding antihistamines (eg, hydroxyzine) are most useful at bedtime and can be used on an as-needed basis, whereas non-sedating antihistamines (eg, fexofenadine) can be used daily throughout the duration of the rash as needed for itch.

There have been recent reports of patients prescribed triple therapy developing more concerning reactions such as DRESS or SJS/TEN.2,10-12 These reactions are known to occur with a higher frequency in patients who have prolonged exposure to an allergy-provoking medication.3,14 As such, regular monitoring for skin pain; mucosal erosions; dyskinesia or blistering; systemic symptoms such as dysphagia, dysuria, or photophobia; and elevations in liver and renal function tests and eosinophil count is critical. Dermatologists are the physicians most comfortable assessing these factors. With the collaborative approach to patient treatment by hepatology and dermatology in this study, no patient had to prematurely discontinue HCV therapy due to a widespread morbilliform eruption, nor were any significant adverse events related to the development of or progression to a grade 3 telaprevir eruption.

The current telaprevir grading system was developed during clinical trials to best quantify and qualify telaprevir-associated eruptions.3-6 The study protocols from these phase II and III trials mandate telaprevir discontinuation in patients with a drug eruption involving 50% or less of their TBSA (grade 2) that is not responsive to therapy or is progressing or a drug eruption involving more than 50% of their TBSA (grade 3).3-6 These guidelines likely developed out of concern that distinguishing a widespread or nonresponsive morbilliform eruption from early DRESS or SJS/TEN may be challenging or beyond the scope of a physician typically prescribing telaprevir. Once telaprevir was shown to be efficacious and approved for use in HCV, these conservative management guidelines were subsequently adopted in the clinical setting despite a lack of evidence supporting their clinical utility.

Given the importance of this medication for patients who have limited therapeutic alternatives for their disease and the ability to safely treat through the eruption as demonstrated in this series, we believe that telaprevir discontinuation is not necessary in all patients with an unresponsive or progressive grade 2 or 3 widespread morbilliform eruption associated with telaprevir. This series suggests that the telaprevir eruption grading system may not accurately translate to the clinical setting. Therefore, we propose a clinical classification of telaprevir-associated eruption that is more consistent with the current dermatologic guidelines for identifying and treating cutaneous reactions to systemic medications that may more accurately reflect patient risk: class 1 (morbilliform) includes any morbilliform or eczematous eruption without evidence of mucosal involvement or systemic inflammation, and class 2 comprises patients with signs and symptoms of DRESS or SJS/TEN (Table 2). We recommend that class 1 eruptions be treated symptomatically, and telaprevir therapy can be continued with close monitoring and frequent follow-up to monitor for the development a class 2 eruption. Early dermatologic consultation may be helpful, particularly in patients with a class 1 widespread morbilliform eruption involving more than 50% of the TBSA, to improve the signs and symptoms of drug eruption as well as aid in safely monitoring for the development of DRESS or SJS/TEN. We agree that all triple therapy must be stopped immediately if a patient develops signs and symptoms of DRESS or SJS/TEN (corresponding to our proposed class 2 eruption), with prompt evaluation by a dermatologist to prevent serious complications.

This study is limited by the inability to distinguish whether patients developed a cutaneous eruption in the setting of telaprevir exposure or another component of triple therapy. In particular, patients 3 and 5 reported a history of a mild pruritic rash to ribavirin and/or pegylated interferon alfa. Given the early recrudescence of their eruptions, it is possible that

<table>
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<tr>
<th>Class of Eruption</th>
<th>Evaluation</th>
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<tr>
<td>Class 1: morbilliform</td>
<td>a. Mild: ≤50% total body surface area</td>
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<tr>
<td></td>
<td>b. Diffuse: &gt;50% total body surface area</td>
</tr>
<tr>
<td>Class 2: DRESS or SJS/TEN</td>
<td>1. Stop all triple therapy immediately 2. Dermatology and/or ED for evaluation and treatment</td>
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</tbody>
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Abbreviations: CBC, complete blood count; DRESS, drug rash with eosinophilia and systemic symptoms; ED, emergency department; LFTs, liver function tests; SJS/TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis.
these patients were again reacting to one of these agents. However, the emergence of a telaprevir-mediated morbilliform eruption within days after treatment initiation has been shown in the literature, and patient 6 in this series also developed a widespread morbilliform eruption within 4 days despite no history of sensitivity to ribavirin or pegylated interferon alfa.

Conclusions

Although more research is needed to explore the pathogenesis of telaprevir morbilliform eruptions, identifying the culprit agent does not alter the results in this series. We recognize that it is certainly reasonable for a hepatologist without training in the assessment of cutaneous disease to discontinue telaprevir in a patient with a progressive and/or widespread eruption if consultation by a dermatologist is not available. Nonetheless, this case series demonstrates that a collaborative effort between hepatologists and dermatologists appears to effectively improve the tolerability of triple therapy treatment. With proper monitoring, it appears that patients with a grade 2 (moderate) telaprevir eruption or uncomplicated grade 3 (severe) telaprevir eruption can safely be treated symptomatically without the need for discontinuation of triple therapy. Given that triple therapy is often the last therapeutic option for patients with HCV, further research to examine this novel approach should be conducted prospectively.

ARTICLE INFORMATION

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Author Contributions: Ms Strazzula and Dr Kroshinsky had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pratt, Kroshinsky.
Acquisition of data: All authors.
Analysis and interpretation of data: Kroshinsky.
Drafting of the manuscript: Strazzula.
Critical revision of the manuscript for important intellectual content: Pratt, Zardas, Chung, Thiim, Kroshinsky.
Administrative, technical, or material support: Chung.
Study supervision: Pratt, Kroshinsky.

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REFERENCES