Telaprevir-Related Dermatitis

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Objective: To evaluate the incidence, type, and severity of telaprevir-associated skin reactions.

Design: Three dermatologists assessed available information including photographs, biopsy results, and clinical summaries of all cases with skin eruptions reported as moderate or severe during the telaprevir clinical development program. For cases from placebo-controlled trials, they were masked to exposure.

Settings: Phase 1 to 3 studies of telaprevir combination therapy for hepatitis C.

Patients: All patients with skin eruptions enrolled in telaprevir clinical trials prior to 2011.

Main Outcome Measures: Incidence, diagnosis, morphologic features, extent, and severity of skin eruption.

Results: Skin eruptions were more frequent in patients who received telaprevir as part of hepatitis C treatment compared with pegylated interferon (peginterferon) and ribavirin alone (56% vs 34% overall; 3.7% vs 0.4% severe). Occurring at any time during the 12 weeks of telaprevir combination regimen, in more than 90% of cases, this eruption is pruritic eczematous dermatitis. None of the clinical or genetic factors examined were substantial risk factors for dermatitis. Three cases of Stevens-Johnson Syndrome (SJS), and 11 cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were suspected, with 2 SJS and 3 DRESS cases considered likely.

Conclusions: Telaprevir-related dermatitis occurs in a majority of telaprevir-treated patients. It is an eczematous dermatitis that differs in timing and appearance from the eruptions usually associated with drug reactions. The strong signal for an increased risk of DRESS or SJS requires particular vigilance in telaprevir-treated patients.


Methods

Data collection and review

Data from 3 international phase 3 studies of telaprevir in combination with interferon and ribavirin were assessed. Study investigators graded reactions by the extent and morphologic features: grade 1 (mild) reactions were localized skin eruptions; grade 2 (moderate), diffuse skin eruptions involving up to 50% of
body surface area; and grade 3 (severe), generalized eruptions involving 50% or more of body surface area or any eruption with bullae, vesicles, purpura, epidermal detachment, or mucous membrane erosions. A special search category that grouped related MedDRA (Medical Dictionary for Regulatory Activities) terms23 was used to capture possible cutaneous reactions.

In the largest phase 3 study, a prospective evaluation of all “rash events of special interest” (ESI) was implemented, defined as any skin eruption leading to treatment discontinuation and all grade 3 skin eruptions. Data collected for ESIs included an investigator-completed form that provided details on the extent, distribution, morphologic features of the eruption, and associated symptoms. The protocol included standardized dermatologic consultations, photographs, skin biopsies, and laboratory studies including serial complete blood cell counts, viral load, and liver function tests. In other phase 3 and laboratory studies including serial complete blood cell counts, viral load, and liver function tests. In other phase 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No. (%)</th>
<th>% Difference Between Telaprevir- and Placebo-Treated Patients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse skin reaction</td>
<td>Telaprevir Plus Peginterferon and Ribavirin (n = 1797)</td>
<td>Placebo Plus Peginterferon and Ribavirin (n = 493)</td>
</tr>
<tr>
<td>Mild</td>
<td>1009 (56)</td>
<td>168 (34)</td>
</tr>
<tr>
<td>Moderate</td>
<td>725 (40)</td>
<td>143 (29)</td>
</tr>
<tr>
<td>Severe</td>
<td>218 (12)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Discontinuation of telaprevir or placebo due to skin eruption</td>
<td>66 (4)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Discontinuation of all drugs due to skin eruption</td>
<td>115 (6)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Discontinuation of all drugs due to skin eruption</td>
<td>15 (1)</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

In phase 3 studies, adverse skin events occurred significantly more frequently with telaprevir plus peginterferon and ribavirin (56%) than with placebo plus peginterferon and ribavirin (34%; 95% CI of risk difference [RD], 17% to 27%) (Table 1). Severe skin reactions were also more frequent in telaprevir-treated patients (3.7% vs 0.4%; 95% CI of RD, 2.0% to 4.3%), as was discontinuation of telaprevir or placebo because of skin complaints (6.4% vs 0.4%; 95% CI of RD, 4.6% to 7.3%). Only 0.8% of telaprevir-treated and 0.4% of placebo-treated patients discontinued all 3 drugs owing to skin eruption (95% CI of RD, −0.6% to 1.1%).

**CLINICAL CHARACTERISTICS**

The panel reviewed a total of 221 cases with skin eruptions, including 151 (68%) with photographs, 131 (59%) with a local dermatologist’s evaluation, and 54 (38%) with skin biopsy results. In the largest controlled study,15 an ESI affected the skin in 56 of 727 patients who received telaprevir (7.7%) and 3 of 361 who received placebo (0.8%; 95% CI of RD, 4.6% to 9.2%). Photographs were available for 45 (80%) and biopsy specimens for 36 (64%) of the 56 telaprevir-related cases.

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**GENETIC INVESTIGATIONS**

Genomic DNA was isolated from peripheral blood mononuclear cells, and quality control was performed according to established standard laboratory procedures. For MDR1 genotyping, polymerase chain reaction (PCR) reagents for single-nucleotide polymorphism assays were obtained from Applied Biosystems Inc and are part of their validated Assay on Demand portfolio. The single-nucleotide polymorphism assay classifies samples as homozygotes (having only allele 1 or 2 [eg, 3435 CC or TT]) or heterozygotes (having both alleles 1 and 2 [eg, 3435 CT]). For HLA typing, DNA from a convenience sample of phase 2 and 3 patients were sent to the HLA Services Laboratory, American Red Cross–Northeast Division. Typing was performed by a high-resolution PCR-based method designed to type patients across 3319 distinct HLA-A, HLA-B, HLA-CW, HLA-DRB, and HLA-DQB loci. Each HLA allele was tested for an association with skin eruption using a 2-sided Wald test for logistic regression with significance level of .01. The odds ratio (OR) with 95% confidence interval and a P value for a Wald test based on the OR were reported for each allele. The Sidak method was used to correct multiple comparisons.4 All studies included in these analyses were approved by an institutional review board or human ethics committee.
Nearly all photographs showed an eczematous component (39 of 41 [95%]) (Figure 1), which we call telaprevir-related dermatitis. Seven (17%) also exhibited maculopapular features, and 4 (10%), papular lichenoid features. Pruritus was reported in 53 of the 56 telaprevir-treated cases (95%). Xerosis, excoriations, and/or lichenification were commonly observed.

Of 36 biopsy specimens obtained from patients treated with telaprevir-based regimen, 34 (95%) showed a spongiotic dermatitic pattern, which most often included epidermal spongiosis and superficial perivascular predominantly lymphocytic infiltrate (Figure 2). Eosinophils were only occasionally present except for 1 case with eosinophil-rich infiltrate. Of the 34 biopsy specimens, 13 (38%) also showed focal, patchy, low-intensity vacuolar interface dermatitis, characterized by a focal, low-density lymphocytic infiltrate along the dermoepidermal interface. No keratinocyte apoptosis or necrosis was seen. These findings were consistent with the eczematous clinical appearance and support the denomination of telaprevir-related dermatitis.

One case (Table 2) with a clinical diagnosis of Stevens-Johnson Syndrome (SJS) exhibited a well-developed interface dermatitis with numerous apoptotic and necrotic keratinocytes (erythema multiforme/SJS pattern).

Table 2. Potential Cases of SJS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/age/country</td>
<td></td>
<td>M/41/US</td>
<td>F/50/Japan</td>
<td>F/56/Japan</td>
</tr>
<tr>
<td>Onset after prescription initiation, wk</td>
<td></td>
<td>19</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Mucosal erosions</td>
<td></td>
<td>Yes (2 sites)</td>
<td>Yes (2 sites)</td>
<td>Yes (2 sites)</td>
</tr>
<tr>
<td>Skin detachment, % BSA</td>
<td></td>
<td>1-2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Histologic finding</td>
<td></td>
<td>Compatible</td>
<td>Suggestive</td>
<td>Not suggestive</td>
</tr>
<tr>
<td>Assessment</td>
<td></td>
<td>Definite SJS</td>
<td>Probable SJS</td>
<td>Possible SJS</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; SJS, Stevens-Johnson syndrome; US, United States.

TIMING AND COURSE OF TELAPREVI R-RELATED DERMATITIS

Telaprevir-related dermatitis occurred at any time after initiating therapy (median, 15 days; interquartile range, 4-41 days). Of the 869 telaprevir plus peginterferon and riba-

virin–treated and 182 placebo plus peginterferon and riba-
virin–treated patients with an initially limited extent of skin involvement, 69 (7.9%) and 4 (1.9%) cases, respectively, progressed to moderate and 18 (2.1%) and 0 cases, re-
Of these 11 patients, 7 were hospitalized. Resolution was assessed case-by-case, and 8 possible cases of DRESS (5 probable and 3 possible) occurred during the course of the telaprevir combination regimen. One definite case of Stevens-Johnson syndrome (SJS) (Table 2). The definite case occurred 11 weeks after the last dose of telaprevir and was considered to be unlikely related to telaprevir. One probable and 1 possible case of SJS occurred during the course of the telaprevir combination regimen.

There were 1 definite, 2 probable (including 1 published case), and 8 possible cases of DRESS (Table 3). Of these 11 patients, 7 were hospitalized. Resolution was documented for 10 of the 11 cases. The remaining patient was lost to follow-up. Of the 11 cases of suspected DRESS, 6 had data available on telaprevir pharmacokinetics. Telaprevir plasma concentrations in suspected DRESS cases did not differ substantially from that of the study population (data not shown). No case of angioedema, anaphylaxis, or vasculitis was observed.

### RISK FACTORS FOR TELAPREVIR-RELATED DERMATITIS

In both univariate and multivariate analyses, the incidence of telaprevir-related dermatitis was significantly higher ($P = .03$) with age above 45 years, body mass index below 30 (calculated as weight in kilograms divided by height in meters squared), white race, and if receiving peginterferon or ribavirin (Table 4). Peginterferon and ribavirin exposures represent observed week 4 or 8 serum and plasma concentrations, respectively.

### SEVERE CUTANEOUS ADVERSE REACTION

Using the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring criteria, we assessed the 221 ESI cases to determine the likelihood that they were severe cutaneous adverse reaction (SCAR) cases. There was 1 definite, 1 probable, and 1 possible case of Stevens-Johnson syndrome (SJS) (Table 2). The definite case occurred 11 weeks after the last dose of telaprevir and was considered to be unlikely related to telaprevir. One probable and 1 possible case of SJS occurred during the course of the telaprevir combination regimen.

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Table 5. Summary of MDR1 Genotype and Severity of Adverse Skin Reaction

<table>
<thead>
<tr>
<th>P-gp Alleles</th>
<th>Subjects Treated With Telaprevir Plus Peginterferon and Ribavirin</th>
<th>Subjects Treated With Peginterferon and Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe Skin Eruption</td>
<td>Mild or Moderate Skin Eruption</td>
</tr>
<tr>
<td>At base 3435</td>
<td>(n = 12)</td>
<td>(n = 11)</td>
</tr>
<tr>
<td>CC</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>TT</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>CT</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>At base 1236</td>
<td>(n = 12)</td>
<td>(n = 11)</td>
</tr>
<tr>
<td>CC</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>TT</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>CT</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviation: P-gp, P-glycoprotein.

subjects to HLA typing and did not experience SCAR. In the primary analysis, 114 patients with skin reaction of any severity were compared with 73 controls without a skin reaction. No association remained significant at the .05 level when $P$ values were corrected for the 143 allele-specific comparisons.

Since HLA associations have been mainly described in severe reactions,23,24 in our secondary analysis, patients with an extensive eruption (n = 59) were compared with those with less-extensive skin eruptions (n = 55) and no eruption (n = 73). Five alleles were significant at the .05 level based on uncorrected $P$ values: 2 alleles (B*4402 [OR, 2.43]; DQB1*0202 [OR, 2.01]) were risk factors for severe skin reactions. After correction for multiple comparisons, none remained significantly associated.

More than 50 single-nucleotide polymorphisms have been identified in the human MDR1 gene, especially at positions C3435T and C1236T, in approximately 40% of the white population.18-20 MDR1 C3435T and C1236T genotypes were determined in patients treated with telaprevir plus peginterferon and ribavirin, who had severe reactions (n = 12), mild or moderate reactions (n = 11), or no reactions (n = 10), and in patients treated only with peginterferon and ribavirin without a skin eruption (n = 11). As given in Table 5, no trend was discerned for the presence of a particular genotype and the severity of skin eruption. Although a homozygous 1236T/3435T haplotype might be a risk factor, most patients were heterozygous (CT) or homozygous (CC) for the 1236 and 3435 alleles in all subgroups independent of the presence, absence, or severity grade of the skin reaction.

COMMENT

Treatment regimens for HCV that include telaprevir in combination with peginterferon and ribavirin frequently result in a pruritic eczematous dermatitis with a spongiosic pattern as the predominant histologic finding, known as telaprevir-related dermatitis. The incidence of dermatitis in telaprevir-treated patients (>50%) is 20% higher than with peginterferon and ribavirin alone. Approximately 9% of patients treated with telaprevir developed extensive eruptions that are infrequent with peginterferon and ribavirin alone. The addition of telaprevir increases the incidence and the severity but does not appear to change the nature of the eruption most commonly observed with peginterferon and ribavirin.

In addition to the frequent occurrence of telaprevir-related dermatitis, cases of severe cutaneous adverse reactions were observed, including 3 suspected cases of SJS and 11 suspected cases of DRESS. Five cases of severe cutaneous adverse reactions (2 SJS and 3 DRESS) were assessed as likely. Given the exposed population (n = 3819), it is likely that the risk of SCAR is increased in patients receiving telaprevir combination therapy. A recent report of 2 possible cases of DRESS observed at a single institution reinforces this concern.27

These observations support the need for education of prescribing physicians, patient monitoring to detect possible SCAR cases early, and prompt treatment withdrawal in suspected cases. The strengths of this evaluation include the prospective collection of data using a standardized questionnaire, the frequent availability of clinical photographs, dermatologic evaluations and skin biopsy specimens, and our being masked to treatment group in the placebo-controlled studies.

The limitations of this study are those inherent to observational studies. It was not possible to evaluate the effect of topical treatments such as emollients or topical corticosteroids that were often prescribed and may have altered the extent of telaprevir-related dermatitis. In addition several laboratory investigations of risk factors (eg, polymorphism of P-glycoprotein coding gene MDR1 and pharmacokinetics measures) were performed on a limited number of patients.

Telaprevir-related dermatitis differs from common drug-induced eruptions in several ways. The incidence (50%-60%) is higher than seen with “drug allergy.”28 Nearly one-fourth of cases began within 4 days, and 46% after 4 weeks—very different timing than that usually observed with most drug-induced eruptions.28 Telaprevir-related dermatitis, which accounts for 95% of skin events in telaprevir-treated patients, is clinically and histologically eczematous and different from the classic “maculopapular” drug-induced eruptions. A recent case report of rapid recurrence of an eczematous eruption with reuse of telaprevir suggests that immunologic mechanisms may
play a role, but this proposed mechanism requires further exploration. While some clinical factors were shown to be associated with an increased risk of eczematous dermatitis, the associations were not very strong and mainly included demographic characteristics that are unlikely to be useful for excluding patients from a treatment because of a small increase in the risk of dermatitis.

No specific HLA alleles or gene variants of MDR1 were associated with skin reactions of any severity. The 1236T/3435T haplotype was expected to result in higher telaprevir exposures. However, this was not observed. Exposures were similar in the 1236T/3435T subjects (minimum steady-state plasma concentration during a dosage interval $C_{\text{min,ss}}$ 2680 + 999 ng/mL) ($n = 5$) compared with subjects with CT or CC 1236/3435 haplotypes ($C_{\text{min,ss}}$ 2280 + 692 ng/mL) ($n = 28$). It is important to note that the genetic analyses were performed on a small number of patients, especially for MDR1 polymorphism.

In clinical practice, telaprevir-related dermatitis is frequent but is most often of limited extent. On the basis of our experience, we suggest that clinicians focus on the following 2 objectives: (1) vigilance for early signs of SCAR that would require immediate discontinuation of all treatment and (2) therapy to alleviate signs and symptoms of telaprevir-related dermatitis to help patients tolerate treatment.

Symptoms and signs of early SJS include skin pain, mucous membrane involvement, vesicles, and a positive Nikolsky sign on dusky macules.

Early diagnosis of DRESS may be challenging. Late-onset cutaneous lesions, extensive confluent eruption, facial edema, temperature above 38.5°C, or lymph node enlargement should prompt laboratory tests including complete blood cell count to detect eosinophilia and/or activated "atypical" lymphocytes, altered serum liver tests, and serum creatinine measurements to detect raised levels, which help confirm the likelihood of DRESS. If SJS or DRESS is suspected, all drug treatments suspected as possible causes, including telaprevir, should be discontinued.

Unfortunately no controlled study is available on the optimal management of telaprevir-related dermatitis. However, the treatments often helpful for contact dermatitis or atopic dermatitis may help to control also the telaprevir-related dermatitis, which shares many clinical and histological characteristics of these conditions.

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Authors Contributions: Drs Roujeau, Mockenhaupt, Tahan, Singhal, Kauffman, and Stern had full access to all of 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: Roujeau, Mockenhaupt, Singhal, Kauffman, and Stern. Acquisition of data: Harding, Bengtsson, and Singhal. Analysis and interpretation of data: Roujeau, Mockenhaupt, Tahan, Henshaw, Martin, Harding, van Baelen, Singhal, Kauffman, and Stern.

Drafting of the manuscript: Henshaw, Harding, Singhal, and Stern. Critical revision of the manuscript for important intellectual content: Roujeau, Mockenhaupt, Tahan, Henshaw, Martin, Harding, van Baelen, Bengtsson, Singhal, Kauffman, and Stern. Statistical analysis: Martin, van Baelen, and Bengtsson. Obtained funding: Singhal and Kauffman. Administrative, technical, and material support: Tahan and Henshaw. Study supervision: Singhal and Stern.

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mad Bsharat, PhD (from Vertex Pharmaceuticals), as-
isted with statistical analysis; Laura Bower, MD (from Vertex Pharmaceuticals), assisted with data compila-
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