**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.

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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) terms\textsuperscript{21} 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 trials and laboratory studies including serial complete blood cell counts, viral load, and liver function tests. In other phase 3 trials, similar forms were completed. Dermatologic evaluations and photographs were encouraged but not required. A “Dermatology Expert Panel” (J.C.R., M.M., and R.S.S.) assessed all patients with an ESI in phase 3 studies. The panel was masked to treatment group (telaprevir or placebo in addition to peginterferon and ribavirin). A single dermatopathologist (S.R.T.) reviewed 53 histopathologic specimens available from 84 skin biopsies.

CLINICAL RISK FACTORS AND PHARMACOKINETICS

Logistic regression analyses were performed on data from 1346 patients treated with telaprevir plus peginterferon and ribavirin and 764 patients treated with placebo plus peginterferon and ribavirin from phase 2 and 3 studies to evaluate predictors of skin eruption. For each of the demographic and baseline disease factors (sex, age, body mass index, region, ethnic group, prior treatment status, and fibrosis category), a bivariate logistic regression analysis was performed including treatment (telaprevir or placebo) and the evaluated factor. Logistic regression analyses were also performed on 556 patients assigned to 12 weeks of telaprevir-based regimen in combination with peginterferon and ribavirin to determine the correlation between skin reaction and plasma concentration of telaprevir, peginterferon, and ribavirin at steady state (week 4 or 8). Univariate logistic regression analysis was performed on each of the exposure factors.

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-DQ\textsubscript{B} 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. All studies included in these analyses were approved by an institutional review board or human ethics committee.

RESULTS

INCIDENCE

In phase 3 studies, adverse skin events occurred significantly more frequently with telaprevir plus peginterferon and ribavirin (36%) 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 84 (38%) with skin biopsy results. In the largest controlled study,\textsuperscript{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.

<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>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 telaprevir or placebo due to skin eruption</td>
<td>15 (1)</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

Table 1. Incidence of Adverse Skin Reactions, Severity Grade, and Discontinuation Due to the Skin Eruption During the Telaprevir or Placebo Combination Treatment in Phase 3 Trials
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>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/age/country</td>
<td>M/41/US</td>
</tr>
<tr>
<td>Onset after prescription initiation, wk</td>
<td>19&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mucosal erosions</td>
<td>Yes (2 sites)</td>
</tr>
<tr>
<td>Skin detachment, % BSA</td>
<td>1-2</td>
</tr>
<tr>
<td>Histologic finding</td>
<td>Compatible</td>
</tr>
<tr>
<td>Assessment</td>
<td>Definite SJS</td>
</tr>
</tbody>
</table>

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

<sup>a</sup>Eleven weeks after telaprevir therapy discontinuation.<sup>15</sup>

<sup>b</sup>Also assessed as a possible case of drug reaction with eosinophilia and systemic symptoms (case 9).

**TIMING AND COURSE OF TELAPREVID-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 ribavirin–treated and 182 placebo plus peginterferon and ribavirin–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-
Table 3. Potential Cases of DRESS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
<th>Case 10</th>
<th>Case 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/age, y/country</td>
<td>¥/60/Japan</td>
<td>¥/53/France</td>
<td>¥/57/France</td>
<td>¥/35/UK</td>
<td>¥/57/France</td>
<td>¥/35/UK</td>
<td>¥/57/France</td>
<td>¥/35/UK</td>
<td>¥/57/France</td>
<td>¥/35/UK</td>
<td>¥/57/France</td>
</tr>
<tr>
<td>Onset, wk</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Temperature &gt;38.5°C</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Extent of skin eruption &gt;50% BSA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
<td>Unknown</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Visceral</td>
<td>Kidney</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Lung</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Eosinophils, %</td>
<td>≥20</td>
<td>≥20</td>
<td>≥20</td>
<td>≥20</td>
<td>≥20</td>
<td>10 to &lt;20</td>
<td>≥20</td>
<td>≥20</td>
<td>10 to &lt;20</td>
<td>≥20</td>
<td>≥20</td>
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<tr>
<td>Atypical lymphocytes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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</tr>
<tr>
<td>Assessment</td>
<td>Definite</td>
<td>Probable</td>
<td>Probable</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
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<td>Unknown</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; UK, United Kingdom; US, United States.

aAlso assessed as probable Stevens-Johnson syndrome (case B).

Table 4. Telaprevir, Peginterferon, and Ribavirin Exposure During the Telaprevir Treatment Phase

<table>
<thead>
<tr>
<th>Skin Reaction Grade During Telaprevir Phase</th>
<th>Telaprevir, ng/mL a</th>
<th>Peginterferon, pg/mL a</th>
<th>Ribavirin, ng/mL a</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>235</td>
<td>3140 (897)</td>
<td>16 400 (8750)</td>
</tr>
<tr>
<td>Mild</td>
<td>217</td>
<td>3120 (957)</td>
<td>16 900 (8510)</td>
</tr>
<tr>
<td>Moderate</td>
<td>84</td>
<td>3060 (866)</td>
<td>16 700 (7230)</td>
</tr>
<tr>
<td>Severe</td>
<td>20</td>
<td>3270 (1030)</td>
<td>17 800 (7030)</td>
</tr>
</tbody>
</table>

Values reported are mean (SD). Telaprevir exposures represent model-derived mean steady-state plasma concentrations. Peginterferon and ribavirin exposures represent observed week 4 or 8 serum and plasma concentrations, respectively.

respectively, progressed to severe. Of 178 telaprevir plus peginterferon and ribavirin–treated and 31 placebo plus peginterferon and ribavirin–treated patients with an initially moderate extent of skin involvement, 12 (0.7%) and 1 (0.3%) cases, respectively, progressed to severe. Resolution of dermatitis was slow (median time to resolution, 44 days [range, 1-504 days]), even among patients who discontinued telaprevir treatment.

Most patients were prescribed emollients and/or topical corticosteroids. In the absence of systematic data collection, assessment of their efficacy on telaprevir-related dermatitis was not possible. Use of systemic steroids required study drug discontinuation per protocol.

SEVERE CUTANEOUS ADVERSE REACTION

Using the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR)23 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.

There were 1 definite, 2 probable (including 1 published case23), 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 therapy for HCV for the first time. However, the impact of these factors on the risk were modest (differences in incidence of telaprevir-related dermatitis between subgroups was always below 20% and most often below 10%)

Pharmacokinetics studies found no statistically significant relationship between the occurrence of extensive skin reactions during the telaprevir or placebo phase and plasma concentration of telaprevir (P = .48), peginterferon (P = .54), or ribavirin (P = .56). Table 4 gives telaprevir exposures by the extent of skin eruption.

A total of 187 patients were included in the HLA analyses. They were treatment-naive white subjects treated with a telaprevir-based regimen in a phase 2 or 3 study, who...
consented 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,25,26 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 In our study, 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.

### 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.

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 MDRI 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\textsubscript{min,ss}] 2680 ± 999 ng/mL) (n = 5) compared with subjects with CT or CC 1236T/3435T haplotypes (C\textsubscript{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 MDRI 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 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 historical 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.
Conflict of Interest Disclosures: Drs Roujeau, Mockenhaupt, Tahan, and Stern served as consultants and received consulting fees from Vertex Pharmaceuticals. Drs Henshaw, Martin, Harding, Singhal, and Kauffman and Mr Bengtsson are employed by Vertex Pharmaceuticals and may hold Vertex Pharmaceuticals stocks and/or options. Dr van Baelen is employed by Janssen Pharma and may hold Janssen Pharma stocks and/or options. Dr Roujean has served on expert panels on severe cutaneous adverse reaction (SCAR) cases for AB Science, Menarini, and US Lawyers; has served on safety boards on SCAR for OM Pharma and Servier; and has received unrestricted research grants (RegiSCAR) from Novartis, GlaxoSmithKline, Boehringer-Ingelheim, OM Pharma, Astellas, and Servier. Dr Mockenhaupt is the coordinator of the international RegiSCAR-project, which is funded by grants from the European Commission (QLRT-2002-01738) and GIS-Institut des Maladies Rares and INSERM (4CH09G) in France and by a consortium of pharmaceutical companies (Bayer Vital, Boehringer-Ingelheim, Cephalon, GlaxoSmithKline, MSD Sharp and Dohme, Merck, Novartis, Pfizer, Roche, sanofi-aventis, Servier, and Tibotec); has received the Else Kröner Memorial Stipendium for support of clinical research through the Else Kröner-Fresenius Foundation; has been an expert in litigations concerning Stevens-Johnson syndrome and toxic epidermal necrolysis; and has served in expert panels and advisory boards coordinated by pharmaceutical companies (2009-2011: dermatology safety board Merck & Co). Currently, RegiSCAR Germany receives funding by the Ministry for Education and Research (Bundesministerium für Bildung und Forschung; grant 01KG1018). Dr Tahan served as a consultant for Tibotec-Jansen Pharmaceuticals. Dr Stern has received consulting fees for the assessment of skin reactions associated with drugs under development from InterMune, Johnson & Johnson, Boehringer Ingelheim, and Takeda and its Millennium Division; has served on a drug-safety panel for Takeda; and has served as an expert witness in product liability litigation relating to skin reactions for Johnson & Johnson and Mutual.
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REFERENCES

1. McHutchison JG, Gordon SC, Schiff ER, et al; Hepatitis Interventional Therapy
Group. Interferon alfa-2b alone or in combination with ribavirin as initial treat-
virin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic
4. Lübke J, Kerl K, Negro F, Saurat JH. Clinical and immunological features of hepa-
5. Charron A, Bessis D, Dureeau O, Guilhou JJ, Guillot B. Local cutaneous side ef-
resulting from the use of interferon and ribavirin. Can J Gastroenterol. 2009;
23(10):877-883.
7. Dereure O, Raison-Peyron N, Larrey D, Blanc F, Guilhou JJ. Diffuse inflamma-
tory lesions in patients treated with interferon alfa and ribavirin for hepatitis C: a
8. Savk E, Uslu G, Karaolgu AO, Sendur N, Karaman G. Diffuse cutaneous eruption
due to interferon alfa and ribavirin treatment of chronic hepatitis C. J Eur Acad
9. Hashimoto Y, Kanto H, Itoh M. Adverse skin reactions due to pegylated inter-
feron and ribavirin combination therapy in hepatitis C patients. J Epidemiol. 2006;
10. Veluru C, Altun I, Chadalavada R, Burns E, Mullen KD. Skin rash during chronic
11. McHutchison JG, Everson GT, Gordon SC, et al; PROVE1 Study Team. Telapre-
vir with peginterferon and ribavirin for chronic HCV genotype 1 infection [pub-
360(18):1827-1838.
2009;360(18):1839-1850.
previously treated chronic HCV infection [published correction appears in N Engl
bination therapy in hepatitis C patients with well-characterized prior treatment
previr for previously untreated chronic hepatitis C virus infection. N Engl J Med.
16. Sherman KE, Flamm SL, Altthal NH, et al; ILLUMINATE Study Team. Response-
guided telaprevir combination treatment for hepatitis C virus infection [published
17. Zeeuem S, Andreone P, Pol S, et al; REALIZE Study Team. Telaprevir for retreat-
18. Fung KL, Gottesman MMA. A synonymous polymorphism in a common MDR1
(ABCB1) haplotype shapes protein function. Biochim Biophys Acta. 2009;1794
(5):860-871.
on the pharmacokinetics and pharmacodynamics of drugs. Pharmacogenomics. 2003;
21. MedDRA MSSO. Medical Dictionary for Regulatory Activities Maintenance and
cessed June 28, 2011.
23. The RegiScar Project. European Registry of Severe Cutaneous Adverse Reac-
tions (SCAR) to Drugs and Collection of Biological Samples. http://regiscar.
eosinophilia and systemic symptoms due to telaprevir. Dermatology. 2010;
221(4):303-305.
HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase in-
26. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-
470-472.
from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive
29. Dupin N, Mallet V, Carlotti A, Vallet-Pichard A, Pol S. Severe skin rash in case of
readministration of telaprevir in a patient who previously experienced a non se-

Correction

Error in “Methods” Text. In the article titled “Association Between Tumor Necrosis Factor Inhibitor Therapy and Myocardial Infarction Risk in Patients With Psoriasis” by Wu et al published online August 20, 2012, and in published in the November issue of the journal (2012; 148[11]:1244-1250), on page 1245, left-hand column, under the subheading “Setting and Participants” in the “Methods” section, first paragraph, the third sentence should have read “The exclusion criterion was a history of MI (ICD-9-CM code 410.xx or 412) documented prior to the third psoriasis diagnosis code.”