

CLINICAL REPORT

High Frequency of Severe Telaprevir-associated Skin Eruptions in Clinical Practice

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Since the introduction of telaprevir, administered in combination with pegylated interferon and ribavirin for the treatment of patients with chronic hepatitis C, the incidence and severity of skin eruptions have increased significantly. The aim of this prospective study is to assess the frequency of drug-induced skin eruptions and their clinical and histological characteristics in patients who received the above treatment in daily clinical practice at our hospital. A total of 60 patients were included. The frequency of telaprevir-associated skin eruptions was 48.3%, which is slightly below, but close to, previously described ranges. There was a predominance of an eczematous clinical pattern, and spongiotic dermatitis on histological examination. A slightly high frequency of severe skin eruptions (13.3%) was found in our study series, which may be explained by all our patients being assessed and closely monitored by one or more dermatologists. **Key words:** hepatitis C; telaprevir; triple therapy; telaprevir-related dermatitis; side-effects.

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Virus hepatitis C (HCV) is a significant health problem, affecting approximately 170 million people worldwide (1). Some years ago, patients with chronic hepatitis C were treated with a combination of pegylated interferon (PEG-IFN) α -2a or α -2b and ribavirin (RBV). However, in 2011 the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved 2 new drugs, telaprevir (TPV) and boceprevir (BPV), for the treatment of chronic hepatitis due to genotype 1 HCV, which is the most frequent genotype in North America and Europe (1–3).

Both TPV and BPV are direct-acting antivirals (DAAs) that inhibit the NS3/4A serine protease, an enzyme essential for viral replication (3, 4). They are indicated for triple therapy in conjunction with PEG-IFN and RBV in adult patients with genotype 1 chronic hepatitis C with compensated liver disease, because this approach has shown greater antiviral effect, lower

resistance rates and a longer sustained viral response (SVR) (1, 5, 6). However, the incorporation of these new drugs has significantly increased side-effects, principally shown in clinical trials (1–3, 7). The incidence of adverse skin effects with the use of TPV has increased to 56%, and the severity has increased to 3.7% (8). However, clinical trials have shown no increase in skin-related adverse effects with BPV (9).

Due to the absence of epidemiological and clinical data in clinical practice, we performed a prospective study to assess the frequency of drug-induced skin reactions and their clinical and histological characteristics in patients who received treatment with PEG-IFN, RBV and TPV for chronic hepatitis due to genotype 1 HCV in daily clinical practice, at Hospital Universitario La Princesa, Madrid, Spain.

MATERIALS AND METHODS

A total of 60 patients who received treatment with PEG-IFN, RBV and TPV were prospectively evaluated at the Dermatology and Digestive Service of Hospital Universitario La Princesa, between February 2012 and December 2014. Of these patients, 29 developed inflammatory skin lesions localized outside the injection sites as a result of the antiviral treatment. Those who had to stop treatment prior to completing the TPV guideline due to lack of response or due to side-effects (different from the cutaneous ones) were excluded.

The following clinical data for these 29 patients were collected: age, sex, onset of antiviral treatment, onset of TPV treatment, HIV co-infection, atopic dermatitis criteria, development of a drug-induced skin reaction, morphological type, symptoms, localization, severity, onset after TPV treatment initiation (in weeks) and suspension of the antiviral treatment (entirely or only TPV) due to the adverse skin effect. Skin biopsies were taken (and analysed by the same pathologist) and their evolution was monitored. Appropriate treatment was prescribed for the skin eruption and, according to the degree of severity of the skin reaction, response to treatment and patient evolution, a decision was made as to whether to suspend the antiviral treatment (TPV only or TPV, PEG-IFN and RBV).

A diagnosis of atopic dermatitis was made based on the diagnostic questionnaire of the UK Working Group on Atopic Dermatitis, Spanish version, validated by Ortiz et al. (10). This questionnaire asked patients about: eczema, persistent pruritus causing them to scratch, asthma symptoms (cough, “wheezing”), allergy to pollen with rhinitis or pruritus of the eyes, and previous diagnosis of atopic dermatitis either in the patient or in their first-degree relatives.

Skin reactions were differentiated according to 3 grades of severity: mild or grade 1 (localized, no vesicles or blisters, no

targetoid lesions, no epidermal detachment, no mucosal erosions or palpable purpura and without systemic symptoms), moderate or grade 2 (diffused covering less than 50% of the body surface, no vesicles or blisters, no targetoid lesions, no epidermal detachment, no mucosal erosions or palpable purpura and without systemic symptoms) and severe or grade 3 (generalized, covering more than 50% of the body surface or presenting vesicles or blisters, targetoid lesions, epidermal detachment, mucosal erosions, palpable purpura and/or systematic symptoms).

Each participant was given written information about the aim of the study. The study was approved by the Clinical Research Ethics Committee at Hospital Universitario La Princesa, Madrid. Written informed consent was obtained from patients.

The patients' data were analysed with a χ^2 test and Student's *t*-test, comparing the group of patients with TVP-associated skin eruption with the group without TVP-associated skin eruption. There were no significant differences between the 2 groups, except that the frequency of females was higher in the TVP-associated skin eruption group ($p=0.045$).

RESULTS

Of the 60 patients who received triple antiviral therapy, 29 were diagnosed with TVP-associated skin eruption (48.3%) (17 men and 12 women, age range 20–66 years (mean 51 years)). Their characteristics are summarized in Table S1[†]. Thirty-one patients did not develop skin eruption (26 men and 5 women, age range 29–66 years (mean 50 years)). In all cases, patients were treated with standard triple antiviral therapy in accordance with recommended guidelines, which include: TPV (750 mg every 8 h with meals for 12 weeks), PEG-IFN (weekly, for 24–48 weeks) and RBV (dosage according to weight, for 24–48 weeks). All patients who developed TVP-associated skin eruptions began the antiviral treatment with the 3 drugs simultaneously, with the exception of 7. Of these, 6 had previously shown no response to PEG-IFN and RBV, and accordingly received dual therapy with PEG-IFN and RBV to evaluate response prior to adding the TPV; 1 received dual therapy for the 4 weeks prior to administering the TPV, in order to evaluate tolerance to the PEG-IFN. All were HIV-negative. None met the criteria for atopic dermatitis.

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Fig. 1. (A) Generalized eczematous eruption with vesicles on the trunk and upper limbs. (B) Close-up of vesicles on the left forearm.

The onset of skin lesions ranged from 1 to 28 weeks after the beginning of the antiviral treatment (mean 9.47 weeks), appearing in 69.6% of patients between the 5th and 12th weeks. The clinical pattern was eczematous (18 patients, 1 with vesicles) (Fig. 1); 5 patients had a maculopapular eruption, 3 urticarial eruption, 1 lichenoid dermatitis, 1 erythema multiforme-like eruption, and 1 developed a drug reaction with eosinophilia and systemic symptoms (DRESS). Skin eruptions were predominantly located on the trunk ($n=20$ patients), upper limbs ($n=17$) and lower limbs ($n=19$) and, less frequently, on the head ($n=10$). The severity of TVP-associated skin eruptions was as follows: mild (grade 1) in 13 patients, moderate (grade 2) in 8 patients, and severe (grade 3) in 8 patients.

Histological examination was performed in 14 of the 29 patients, showing in all cases a mononuclear, perivascular inflammatory infiltrate in the papillary dermis, accompanied by spongiosis in 7 patients (1 with vesiculation) and abundant eosinophils in 2 patients (Fig. S1[†]).

Antiviral treatment had to be suspended due to the skin eruption in 6 patients; all 3 antiviral drugs were suspended for 2 patients, while for the remaining 4 only TPV was suspended and dual therapy with PEG-IFN and RBV was continued.

DISCUSSION

The frequency of skin eruptions in relation to TPV, administered as part of triple therapy according to daily clinical practice in our series, is 48.3% (29/60). This frequency is less than that described in phase 3 of clinical trials with triple therapy including TPV, which was 56% in a US/EU group (8) and 74.9% in a Japanese group (11). These slightly higher rates observed in clinical trials may be due to excessive reporting of skin eruptions, considering that all adverse effects occurring in clinical trials should be reported, even those that may not be due to the drug. Another explanation could be that patients who receive a prescription for TPV in daily clinical practice are advised to use specific skincare and apply emollients, since a high risk for skin eruptions in relation to TPV use is already known. More recent publications

report rates of between 71.43% (25/35) (12) and 44% (70/159) (5). Orrin et al. (12) analysed the rate of skin reactions due to TPV both in patients included in clinical trials and those treated as part of the UK Expanded Access Programme. In this report only 14 of the patients presenting a skin eruption were assessed by a dermatologist. Smith et

al. (5) performed a retrospective observational study of a larger number of patients, although none of these patients was assessed by a dermatologist. On the contrary, in our series, all patients were assessed and followed-up by at least one dermatologist, whether or not they presented with a drug-induced skin eruption.

The majority of patients developed a pruritic eruption that was eczematous in appearance, similar to published descriptions, which some authors have dubbed telaprevir-related dermatitis (8). Although this type of skin eruption is the most common (8, 11), cases of urticarial reactions have also been described similar to that seen in 3 of our patients (13). In our series, 69.6% of patients presented with skin eruptions between the 5th and 12th week from onset of the antiviral treatment (mean 9.47). This latency of onset of skin eruptions has also been described in the literature, with 70% (11) and 46% (8) of patients presenting with skin eruptions from the 4th week of treatment. Also, as described in the literature (11), the locations of skin eruption sites were predominantly the trunk, and the upper and lower limbs, with lower frequency on the head.

The frequency of severe skin reactions in our series is 13.3% (8/60); slightly higher than described in the literature, where the severity of skin reactions related to TPV varies in the different studies: 3.7% in the US/EU group (8), 9% in the Japanese group (11), and 5.7% (2/35) as shown by Orrin et al. (12). In our series, 1 patient developed DRESS (14), fewer than 20 cases of which have been published thus far (8, 15). Other potentially fatal severe adverse skin reactions have been described with this drug, such as Stevens-Johnson syndrome, erythema multiforme-like eruption, toxic epidermal necrolysis or acute generalized exanthematous pustulosis (1, 8, 11, 16).

As regards histological examination, the pattern of spongiotic dermatitis should be noted with a superficial perivascular infiltrate, with a predominance of lymphocytes in 53.8% of our patients, of whom only 15.4% showed abundant eosinophils. There are virtually no published histological descriptions of TVP-associated skin eruptions. Roujeau et al. (8) obtained 36 skin biopsies of patients who developed skin eruptions during antiviral triple therapy with TPV: 95% showed a spongiotic dermatitis pattern. In agreement with these authors, our histological findings are compatible with the eczematous clinical appearance and support the use of the term telaprevir-related dermatitis (8).

In our series, 10% (6/60) of the patients had to suspend antiviral treatment due to adverse skin effects: in 6.7% of cases only TPV was removed (4/60), and in 3.3% of cases all drugs were removed (2/60). Variable rates of treatment suspension have been published elsewhere: in the US/EU group (8), treatment with TPV was suspended in 6.4% of cases, and treatment with all drugs in 0.8% of cases, while in the Japanese group (11), treatment was suspended in 8.6% of cases: 4.1% just TPV and 4.5% all

drugs. Orrin et al. (12) suspended treatment with TPV in only 1 patient (2.8%), whilst Smith et al. (5) suspended antiviral treatment in 4% of patients. A different appreciation of the severity of cutaneous reactions may explain the slightly different suspension rates.

The authors declare no conflicts of interest.

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