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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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 systemic 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 χ2 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 S11. 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.

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 vesication) and abundant eosinophils in 2 patients (Fig. S11). 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

Fig. 1. (A) Generalized eczematous eruption with vesicles on the trunk and upper limbs. (B) Close-up of vesicles on the left forearm.
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 exanthemeus pustulosis (I, 8, 11, 16).

As regards histological examination, the pattern of spongiosic 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 spongiosic 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.

REFERENCES