DOI: http://dx.doi.org/10.3315/jdcr.2014.1183

Journal of Dermatological Case Reports

Dermatologic adverse events of protease inhibitor-based combination therapy in patients with chronic hepatitis C

Elżbieta Kłujszo[1], Piotr Parcheta[1], Dorota Zarębska-Michaluk[2], Ewa Ochwanowska[3], Anna Witkowska[4], Adriana Rakowska[5], Lidia Rudnicka[5], Wiesław Kryczka[2]

1. Department of Dermatology Provincial Hospital, Kielce, Poland;
2. Department of Infections Disease Provincial Hospital, Kielce, Department of Health Science, Jan Kochanowski University, Kielce, Poland;
3. Department of Animal Physiology, Jan Kochanowski University, Kielce, Poland;
4. Student of Medicine faculty, University of Szeged, Hungary;
5. Department of Dermatology, Medical University of Warsaw, Poland.

Corresponding author:

Lidia Rudnicka, MD, PhD

Department of Dermatology
Medical University of Warsaw

Koszykowa 82A

02-008 Warszawa, Poland

E-mail: *lidiarudnicka@gmail.com*

Key words:

boceprevir, interferon, itch, liver, peginterferon, skin, telaprevir, viral infection

Abstract

Background: Combination therapy with pegylated interferon, ribavirin and a first-generation NS3/4A protease inhibitor, telaprevir or boceprevir, is the new strategy for treatment of genotype 1 chronic hepatitis C virus infection. This combination improves therapeutic efficacy but it also increases the risk of adverse events.

Objective: The aim of the study was to analyze frequency and severity of dermatological adverse events during protease inhibitor-based therapy and to evaluate the risk factors for their development.

Patients and methods: This is a retrospective study of 109 patients with genotype 1 chronic hepatitis C treated with boceprevir (n=33) or telaprevir (n=76) based triple therapy. A logistic regression for relationship between clinical, demographic and laboratory factors and cutaneous adverse events was performed.

Results: Dermatological adverse events (skin rash, pruritus, anorectal paresthesia) occurred in both treatments (boceprevir and telaprevir) with similar frequency: 28% in telaprevir and 21% in boceprevir. In patients treated with telaprevir, men were more predisposed to develop skin rashes compared to women (OR 4,1 p=0,014) and age above 45 years was associated with occurrence of pruritus in men (OR 8,16 p=0,014). Being a female, coexistence of autoimmune thyroiditis and advanced liver fibrosis were independent factors predisposing to development of anorectal paresthesia (OR 4,13 p=0,041, OR 4,25 p=0,029, OR 4,54 p=0,018 respectively) in this group. In patients treated with boceprevir, coexistence of autoimmune thyroiditis predisposed to skin rashes (OR 10,22 p=0,017) and being a female predisposed to pruritus (OR11,2 p=0,033). The adverse events occurred after a mean time of 8,6 (range 1—24) weeks after initiation of therapy.

Conclusions: In patients with chronic hepatitis C who received the triple therapy, the anorectal paresthesias were observed only in patients treated with telaprevir. The predisposing factors for this adverse event were: female gender and advanced liver fibrosis. The risk factors for other dermatological adverse were: 1) being a male over 45 years, for skin rashes and pruritus (for telaprevir), 2) coexistence of autoimmune thyroiditis for skin rashes (for boceprevir), 3) being a female, for pruritus (for boceprevir). (*J Dermatol Case Rep*. 2014; 8(4): 95-102)

Introduction

Telaprevir (TVR) and boceprevir (BOC) belong to the group of first generation HCV protease inhibitors (PIs) that were recently approved for the treatment of genotype 1 chronic hepatitis C (CHC). They are peptidomimetic inhibitors of the HCV non-structural (N/S) 3/4A serine protease.[1] Addition of protease inhibitor to the therapy with Peg-interferon alpha (PEG-INF) and ribavirin (RBV) substantially improves therapeutic effects.[2-4] However, such therapy is associated with high risk of dermatological adverse events (DAEs) as well as others adverse events.[5] Monotherapy with interferon has well known DAEs. Distinguishing between HCV-associated dermatological conditions and post-treatment DAEs in terms of causality may be difficult.[6] The 13% incidence of "dermatitis" associated with PEG-INF monotherapy increased to 21% in combination with RBV.[7-9] The DAEs associated with triple therapy using TVR during the phase II/III clinical trials involving over 3800 patients have been reported with a higher frequency and more severe presentations than seen with dual therapy PEG-INF/RBV (56% of patients in triple therapy compared to 34% in dual therapy).[2,3,5,10-13] Because of high rates of DAEs noted in phase II trials of TVR, a grading system and management protocol was implemented for the future use in clinical trials.[14] Grading rash events into four grades is shown in Table 1. In accordance with this guidance DAEs that could be classified as SCAR (severe cutaneous adverse reactions) authorize immediate discontinuation of treatment (TVR, RBV and PEG-INF). The spectrum of SCAR includes 3 variants: Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) also known as drug induced hypersensitivity syndrome (DIHS), and acute generalized exanthematous pustulosis (AGEP).[15-17] There is more data available regarding the safety profile of the PIs from "real-life" and this data revealed increased risk for severe complications of PI-based treatment in cirrhotic patients.[18-21] However skin adverse reactions in contrast with other adverse events were comparable with results in clinical trials.[18,22]

Objective

In our study we collected data regarding the cutaneous adverse event profile of PIs (TVR and BOC) and evaluated the risk factors for developing DAEs during the triple therapy.

Materials and methods

The study involved 109 patients with genotype 1 CHC. All patients were assigned to triple therapy with peginterferon α (PEG-IFN) and ribavirin (RBV) combined with NS3/4A serine protease inhibitor of hepatitis C virus boceprevir (BOC) or telaprevir (TVR) from December 2011 through September 2014. The group consisted of 60 females (55%) and 49 males (45%) aged between 23 and 77 years (mean 52.41 years). All patients received an antiviral therapy in accordance with standard treatment guidelines and Polish Health Care System program recommendations.[23,24]

We analyzed selected laboratory parameters which were performed prior to the commencement of therapy: activity of alanine transaminase (ALT) aspartate transaminase (AST), gamma-glutamyl transferase (GGTP) in serum (labeled by an enzymatic and kinetic method), hemoglobin concentration (Hb), number of neutrophils, platelets, serum total protein, albumin, gamma-globulin, immunoglobulin G (IgG). Other clinical parameters were also analyzed: presence of autoimmune thyroiditis (AT) defined as increased levels of thyroid peroxidase antibodies (a/TPO>ULN) and/or thyroglobulin antibodies (a/TG>ULN), cryoglobulinemia in which immunoglobulins in the blood precipitate at +4°C and dissolve at higher temperatures. The stage of liver fibrosis was determined based on liver biopsy or FibroScan® examination. Patients qualified for antiviral therapy underwent a liver biopsy and the stage of fibrosis was based on Ishak scale. Patients with liver biopsy contraindications underwent FibroScan examination. Three stages of liver cirrhosis were established. 0-1 points of Ishak scale or stiffness of up to 7.0 Kpa in elastographic studies were referred to as absence or minimal liver fibrosis (class 1 of liver fibrosis); 2-3 points in Ishak scale and stiffness of 7.0-9.5 Kpa were referred to as mild liver fibrosis (class 2 of liver fibrosis); 4-5/6 points in Ishak scale and stiffness of more than 9.5-9.6/14.5 Kpa were referred to as moderate/severe liver fibrosis/cirrhosis (class 3 of liver fibrosis).[25] Also, the starting viral load of HCV RNA was measured using GeneProof HCV Real Time PCR kit.

Previous antiviral treatments were also taken into consideration in our study (we distinguished previously treated patients from naïve patients), as well as the kind of interferon used: peginterferon α 2a or 2b. Patients were divided into 2 groups: 1) patients treated with PEG-INF/RBV/TVR (n=76; 70% of the analyzed cohort study), including 42 women and 34 men, and 2) patients treated with PEG-INF/RBV/BOC (n=33; 30%), including 18 women and 15 men.

Baseline characteristic of patients is shown in Table 2. Before the commencement of therapy patients were informed about the importance of special skincare: the use of emollients, mild cleaning agents, avoidance of sun exposure and the use of sun protection such as SPF 50 sunscreens. Safety of therapy was evaluated by closely monitoring any side effects. In those cases where dermatological adverse events (DAEs) appeared, patients were referred to a dermatologist, who then characterized and determined the grade of skin lesions according to the Grading of telaprevir-associated rash severity in Phase III telaprevir trials (Table 1).[14]

Statistical analysis

For quantitative variables (laboratory values) the arithmetic mean (x) and standard deviation (SD) was calculated. The demographic and clinical parameters (Table 1) were expressed as the absolute number and proportions. Blood parameters were categorized according to the thresholds used to define eligibility in a randomized trial of protease inhibitor-based

Table 1. Grading of skin rashes n clinical trials.[14]

Grade	Description
Grade 1 (Mild)	Localized skin eruption and/or a skin eruption with limited distribution, with or without associated pruritus
Grade 2 (Moderate)	Diffuse skin eruption involving up to approximately 50% of body surface area with or without superficial skin peeling, pruritus, or mucous membrane involvement with no ulceration
Grade 3 (Severe)	Generalized rash involving either >50% of body surface area, Or rash presenting with any of the following characteristics: • Vesicles or bullae • Superficial ulceration of mucous membranes • Epidermal detachment • Atypical or typical target lesions • Palpable purpura/non-blanching erythema
Life-threatening or Systemic reactions	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme

Table 2. Baseline characteristics of the patients.

	Total (N = 109) N (%); mean (±SD); median (range)	Boceprevir BOC (N = 33) N (%); mean (±SD); median (range)	Telaprevir TVR (N = 76) N (%); mean (±SD); median (range)
Male gender	49 (45%)	15 (45%)	34 (45%)
Female gender	60 (55%)	18 (55%)	42 (55%)
The presence of crioglobulin	54 (49,5%)	14 (42%)	40 (53%)
Autoimmune thyroiditis	23 (21%)	7 (21%)	16 (21%)
Drug - peginterferon alfa-2B	18 (17%)	7 (21%)	11 (14%)
Drug - peginterferon alfa-2A	91 (83%)	26 (79%)	65 (86%)
Age - years	52 (±11,8)	50 (±12,5)	52,6 (±11,5)
Age > 45 years	83 (76%)	22 (67%)	61 (80%)
Severity of fibrosis minimal	1(0,9%)	—	1 (1,3%)
moderate	66 (61%)	25 (76%)	41 (54%)
advanced/cirrhosis	42 (38%)	8 (24%)	34 (45%)
Naive – without therapy	18 (17%)	9 (27%)	9 (12%)
HCVRNA output (IU/mL)	941383,9 (±119658,1) M; 44600; R:2193,0-5680000	696524,3 (±100069,3) M: 277000,0 R: 2193,0-3390000	1047705 ((±1263609) M: 478943,0; R: 5075-5680000
AST (UI/ml)	77,7 (20-330)	77,5 (20-246)	78 (25-330)
AST (> 100 UI/ml)	28 (26%)	10 (30%)	18 (24%)
ALT (UI/ml)	95,8 (16-388)	92,1 (16-388)	97 (23-345)
ALT (> 100 UI/ml)	39 (36%)	12 (36%)	27 (36%)
GGTP (UI/ml)	91,1 (12-436)	82,6 (12-239)	95 (17-436)
GGTP (> 100 UI/ml)	37 (34%)	10 (30%)	27 (36%)
Hb (g/dL)	14,5 (10,8-18,4)	14,2 (10,8-17)	15 (11,8-18,4)
Hb (g/dL)*	8 (7%)	5 (15%)	3 (4%)
Neutrophils (/µl)	2622,3 (750-5280)	2590,3 (1330-5000)	2636,2 (750-5280)
PLT (/µl) Platelets	163856 (50700-314000)	161036,3 (56900-314000)	165080 (50700-303000)
Platelets (< 100000 /µl)	22 (20%)	7 (21%)	15 (20%)
Total protein (g/dl)	7,1 (5,3-9,1)	6,8 (5,8-8,3)	7,2 (5,3-9,1)
Albumin (g/dl)	4,2 (3,03-5,8)	4,0 (3,0-4,8)	4,2 (3,03-5,8)
Albumin (≤ 3,5 g/dl)	9 (8%)	2 (6%)	7 (9%)
Gamma globulin (g/l)	1,3 (0,3-3,0)	1,1 (0,65-2,1)	1,3 (0,36-3,0)
IgG (g/l)	14,3 (4-26)	12,2 (8-23)	15,5 (4-26)

** Hemoglobin level: ≤ 12g/dl for females and ≤ 13g/dl for males.*

triple therapy.[18] Univariable and multivariable logistic regression models were built to determine baseline factors (clinical, demographic and laboratory) associated with each DAEs. A p value of less than 0,05 was considered significant. Data were analyzed using Statistica 10.0 package [StatSoft, Inc.].

The study was approved at the local ethics board.

Results

Adverse dermatological events occurred in both therapeutic groups. Skin rashes and pruritus occurred in both groups and anorectal discomfort only developed in TVR group. The complete characterization of the skin rashes and anorectal discomfort is presented below. The skin rashes were observed in 28 patients (25,6%) including 14 female (23,3%) and 14 male (28,5%). Pruritus appeared in 36 patients (33,0%) including 20 female (33,3%) and 16 male (32,6%). The isolated (i.e., without skin rash) pruritus was observed in 8 patients (6 female and 2 male) and in the remaining 28 patients skin rashes accompanied pruritus. The anorectal discomfort occurred only in patients treated with TVR. This group included 15 patients (13,7%) including 12 female (20%) and 3 male (6,12%). The distribution of DAEs in both groups of patients (receiving the treatment including either TVR or BOC) is shown in Fig 1. There were no statistically significant differences in frequency of skin rashes between TVR and BOC groups (p=0,481 test Chi^2), but the DAEs in BOC group were less severe.

The distribution of severities of skin rashes based on the adopted grading system in both therapeutic groups is presented in Table 3. None of the patients presented with the most severe form — life threatening systemic reaction.

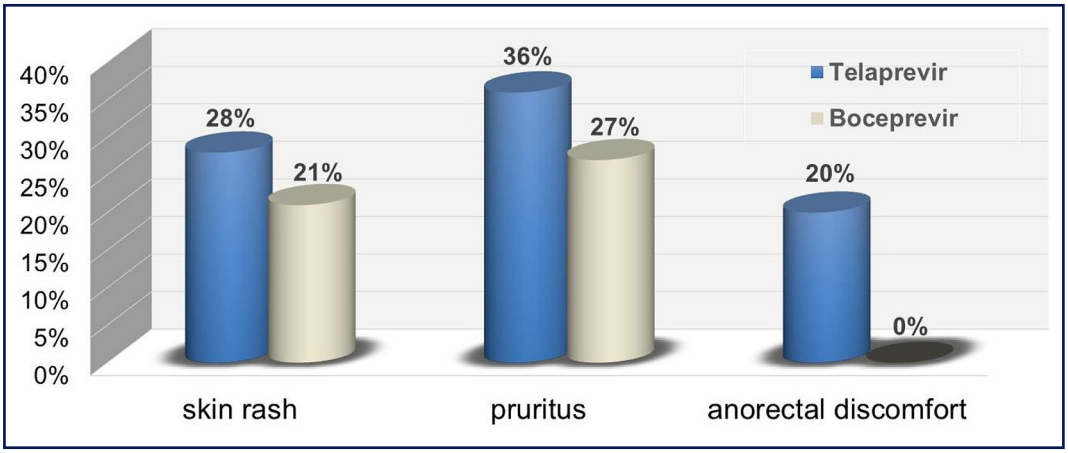

Figure 1

The frequency of dermatological adverse events in patients treated with triple therapy with boceprevir and telaprevir.

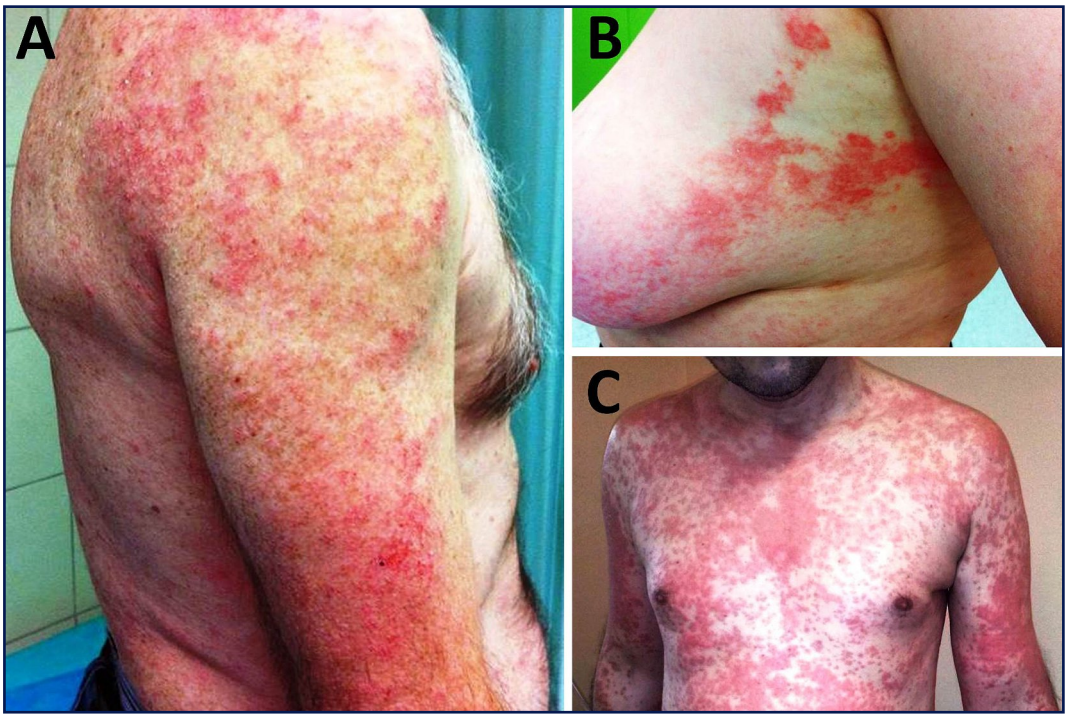

Figure 2

Examples of skin rashes in patients receiving the PIs based triple therapy (A, B, C).

Table 3. The distribution of severities of skin rashes based on the adopted grading system in both therapeutic groups.

Skin Rash	Telaprevir (N=76)	Boceprevir (N=33)	Total (N=109)
Grade 1	9 (12%)	4 (12%)	13 (12%)
Grade 2	9 (12%)	2 (6%)	11 (10%)
Grade 3	3 (4%)	1 (3%)	4 (3,6%)
Summary (G1+G2+G3)	21 (28%)	7 (21%)	28 (25,6%)

Table 4. Univariate and Multivariate logistic regression analysis.

	Total (N=109) OR (95% CI)	p ≤ 0,05	Boceprevir BOC (N = 33) OR (95% CI)	p ≤ 0,05	Telaprevir TVR (N = 76) OR (95% CI)	p ≤ 0,05
Factors related to Skin Rash	N=28(25,6%)		N=7(21%)		N=21(28%)	
Female	0,760 (0,318-1,8)	0,534	7 (0,671-72,9)	0,09	*0,240 (0,074-0,772)	0,014
Male	1,31 (0,549-3,4)	0,534	0,142 (0,013-1, 48)	0,09	*4,1 (1,29-13,3)	0,014
Age - years	1,01 (0,98-1,05)	0,329	0,980 (0,91-1,05)	0,555	*1,06 (1,0-1,1)	0,034
Age > 45 years	1,61 (0,536-4,8)	0,39	0,592 (0,09-3,52)	0,549	2,94 (0,587-14,7)	0,182
Autoimmune thyroiditis	2,26 (0,841-6,1)	0,101	10,22 (1,38-75,4)	0,017	1,25 (0,368-4,24)	0,715
The presence of crioglobulins	0,575 (0,234-1,4)	0,221	0,433 (0,065-2,88)	0,367	0,607 (0,212-1,73)	0,343
AST (> 100 UI/ml)	0,395 (0,122-1,2)	0,117	—	—	0,689 (0,194-2,4)	0,558
ALT (> 100 UI/ml)	0,789 (0,313-1,9)	0,611	—	—	1,54 (0,54-4,4)	0,41
GGTP (> 100 UI/ml)	0,555 (0,208-4,8)	0,233	—	—	0,85 (0,288-2,5)	0,764
Hb (g/dL)*	0.391 (0,044-3,4)	0,39	0,916 (0,077-10,79)	0,942	—	—
Neutrophils (< 1000/µl)	—	—	—	—	—	—
Platelets (< 100000/µl)	0,564 (0,170-1,8)	0,343	—	—	0,919 (0,251-3,3)	0,897
Albumin (≤ 3,5 g/dl)	0,880 (0,168-1,6)	0,879	—	0,998	1,17 (0,202-6,8)	0,853
Factors related to Pruritus						
Female	1,03 (0,458-2,3)	0,939	11,2 (1,09-114,2)	0,033	0,293a* (0,098-0,871) 0,297b (0,099-0,891)	0,024a 0,027b
Male	0,969 (0,428-2,1)	0,94	0,089 (0,008-0,910)	0,033	3,40a* (1,14-10,1) 3,36b (1,12-10,0)	0,024a 0,027b
Age per year	1,02 (0,987-1,06)	0,198	0,972 (0,912-1,03)	0,376	1,07b* (1,01-1,13)	0,011
Age > 45 years	1,8 (0,674-5,2)	0,22	0,514 (0,099-2,6)	0,41	8,16a* (1,46-45,4)	0,014
The presence of crioglobulin	0,731 (0,321-1,6)	0,45	0,545 (0,101-2,9)	0,876	0,777 (0,293-2,05)	0,606
Factors related to Anorectal Discomfort						
Female					4,13 (1,03-16,4)	0,041
Male					0,241 (0,060-0,965)	0,041
Advanced liver fibrosis					4,54 (1,26-16,2)	0,018
The presence of crioglobulin					2,0* (0,563-7,5)	0,264
Autoimmune thyroiditis					4,25* (1,13-15,9)	0,029

** Multivariate logistic regression gender/age interaction.*

The most common skin rashes reported during the study were characterized as mild or moderate (24 patients — 85,72%). The morphological pattern of skin rashes was similar in all patients. The skin rashes had a form of maculopapular eruption, merging at places into extensive erythematous areas with delicate scaling. This typical clinical pattern was described as eczematous dermatitis (Fig. 2). It was observed in 26 patients. One patient developed macular exanthema. Another patient presented with papules and small nodules with ulcerations located mainly on upper extremities. The rashes classified as Grade 3 had typical maculo-papular patterns in most of the cases except one patient with target lesions and 2 patients with facial edema. None of the patients developed lesions on mucous membranes. The localization of skin rashes was similar in all patients and usually affected the extensor surfaces of upper and lower extremities and the trunk. The surface area of skin rashes differed in individual patients; in all patients with Grade 3 rashes more than 50% of the skin was affected. All patients with skin rashes experienced pruritus. Anorectal discomfort was manifested by itching and burning sensations. Skin rashes appeared at different times after the therapy induction, on average after 8,6 weeks (mean 8,6 ± 5,29; min. 1 week max. 24 weeks).

Therapy of skin rashes included oral or parenteral antihistamines, topical glucocorticoid creams and emollients. Patients with severe skin rashes of Grade 3 were given parenteral glucocorticoids for few days. Antiviral therapy was not discontinued in any patients with mild or moderate skin rashes (Grades 1 or 2). The therapy with TVR was withdrawn in 2 patients due to Grade 3 skin rash. In 1 out of 4 patients with severe skin rash of Grade 3 the therapy was not discontinued due to the fact that the skin rash appeared in the last days of PIs therapy. In one of the patients receiving BOC, therapy was not discontinued in the presence of Grade 3 skin rash because the benefits of therapy outweighed the risks in patient's case. In two patients treated with TVR and Grade 3 skin rash the therapy was discontinued because of the severity of side effects. In addition to skin rash, 1 patient experienced systemic side effects: facial edema, eosinophilia (30%) and fever (38.9˚C), and was qualified as "possible case" of DRESS syndrome. Because the symptoms did not meet the confirmation criteria of "definite case" of DRESS syndrome (according to scoring system for classifying DRESS cases as definite, probable, possible or no case from Kardaun *et al*,[17] patient was considered to have skin rash of Grade 3 and continued treatment with PEG-INF/RBV until the end of the therapy. Another patient with skin rash Grade 3, who interrupted TVR therapy had extensive skin lesions affecting more than 50% of her body surface area but without systemic symptoms. All patients who stopped the treatment experienced regression of skin lesions.

The relationship between clinical and demographic factors as well as laboratory baseline parameters (including categorization of blood parameters see Table 1) with the occurrence of DAEs was analyzed with the use of univariate and multivariate logistic regression. Logistic regression included 109 patients who used the triple therapy (Table 4). Anorectal discomfort occurred only in patients treated with TVR (20% versus 0% treated with BOC; p=0.005). Its occurrence was observed to be more frequent in females than in males (OR 4,13 in 95% confidence interval: 1,03-16,4, p Wald test=0,041). Anorectal discomfort occurred more often in patients with advanced liver fibrosis (OR 4,54 in 95% CI: 1,26-16,2, p Wald test=0.018) and with the coexistence of autoimmune thyroiditis (OR 4,25 in 95% CI: 1,13-15,9, p Wald test=0,029). Pruritus occurred more often in women than in men during BOC treatment (OR 11.2 in 95% CI: 1,09-114,2 p Wald test=0.033). In BOC group we also observed predisposition to skin rashes associated with coexistence of autoimmune thyroiditis (OR 10,22 in 95% CI: 1,38-75,4 p Wald test=0.017). In TVR group we observed greater predisposition for skin rashes among men (OR 4,1 95% CI: 1,29-13,3 p=0,014) and for pruritus, which was correlated with male gender (OR 3,40 in 95% CI: 1,14-10,1, p Wald test=0,024) and age above 45 years (OR 8,16 in 95% CI: 1,46-45,4 p Wald test=0,014). The chance for skin rashes increased by 0,034 for each year increase (OR 1,06 95% CI: 1,0-1,1) as well as the chance for development of pruritus during TVR therapy increases by 0,011 for each year increase (OR 1,07 95% CI: 1,01-1,13). There were no statistically significant differences for other demographic and clinical factors as well as laboratory baseline parameters.

Discussion

In our study, the frequency of DAEs was lower than in data from clinical trials.[5,12-14] DAEs in both treatments (TVR, BOC) together occurred in 25,6% of patients. The data from clinical trials with TVR presented that the 55% and 51% of patients developed rash and the pruritus, respectively, during the triple therapy, compared with 33% and 26% on placebo with PEG-INF and RBV.[14] DAEs, which were observed, had a similar clinical pattern: pruritus, xerosis, erythematous papules, vesicles and excoriated lesions located on the trunk, extremities and friction sites. It could be more accurately described as eczematous dermatitis.[14] The lower percentage of DAEs in our study could be a result of intentional directing patients towards proper skin care, photo protection with high SPF sun screeners and sun avoidance prior to commencing the therapy. The percentage of rash grade 3 was identical in both groups. 14,3% of rashes equally in TVR and BOC group was classified as grade 3. In total, grade 3 rash occurred in 3,67% of treated patients. DAEs (grade 3 rash) in our study was the reason for cessation of TVR only in two patients, however there was no need to withdrawal of PEG-INF and RBV, therefore these patients could complete required treatment. Rash grade 3 arisen in one patient treated with BOC (it was classified as grade 3 because of area more than 50% involved) and there was no need for cessation of BOC. Previous data from clinical trials reported DAEs in triple therapy based on TVR more frequent than in BOC (in BOC therapies they were reported with the same frequency as in the dual therapy with PEG-INF and RBV and there was no case of SCARs).[14,26-28] Cases of SCARs occurred only in TVR group during clinical trials and they were also reported in post registration's studies.[12,14,26,29-35]

However, the first case of DRESS syndrome during therapy with BOC was described in 2012.[36] In our study there was similarity in frequency of DAEs in BOC and TVR groups (28% in TVR group and 21% in BOC group (p=0,481 test Chi^2) however the intensity of DAEs was milder in BOC group. In our study anorectal discomfort was present only in TVR treated group in 20% of patients. Such complaints were reported in clinical trials for instance in REALIZE study, where 28% patients experienced anorectal discomfort.[11] We did not find any case of anorectal disorder in the BOC treated group, similar as in clinical trials, however there are reports of single cases in post registration clinical practice.[22] There was no requirement for discontinuation of TVR due to anorectal complaints in our series. All symptoms disappeared after completed therapy. Advanced liver fibrosis was found to be an adverse event associated with anorectal discomfort in Bichoupan *et al*. study.[20] We also found such correlation (OR 4,54 p=0,018). This finding could be due to immune compromise in patients with advanced fibrosis.[37]

We have not observed increased occurrence of DAEs although, patients were enrolled to the study without stringent criteria normally applied in clinical trials. Percentage of advanced (grade 3) liver fibrosis in our study reached 38,6% and was substantially higher than in registration trials (10-28% of patients).[21] The demographic factors that have an influence on development of DAEs in our study were similar with findings in other studies.[12]

The association between coexistence of autoimmune thyroiditis with skin rashes during BOC therapy as well as, correlation between comorbidity of AT with anorectal discomfort were not previously observed.

Alternations in baseline levels of laboratory parameters in our cohort did not increase the risk of DAEs although in the multicenter French study CUPIC the risk of death or severe complications according to serum albumin level and platelet count was identified.[18]

Conclusions

DAEs occurring during the PIs based triple therapy are usually mild to moderate. The anorectal complaints were observed only during TVR therapy. Advanced liver fibrosis and comorbidity of autoimmune thyroiditis predisposed to development of anorectal discomfort in this group. Contributing factors to DAEs during the triple therapy according to our study were: 1) being a male and age over 45 years, for skin rashes and pruritus during TVR therapy, 2) coexistence of autoimmune thyroiditis, for skin rash during BOC therapy, 3) being a female, for pruritus during BOC therapy.

Appropriate training concerning skin care before the commencement of therapy and monitoring of skin condition mitigates DAEs, which consequently leads to effective therapy of more patients with chronic hepatitis C. Cooperation between hepatologists and dermatologists may improve the safety of triple therapy.

References

1. Rajani AK, Ravindra BK, Dkhar SA. Telaprevir: changing the standard of care of chronic hepatitis C. *J Postgrad Med*. 2013; 59: 42-47. PMID: 23525057.
2. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med*. 2009; 360: 1827-1838. PMID: 19403902.
3. Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourlière M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med*. 2009; 360: 1839-1850. PMID: 19403903.
4. Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, Davis MN, Galati JS, Gordon SC, Ravendhran N, Rossaro L, Anderson FH, Jacobson IM, Rubin R, Koury K, Pedicone LD, Brass CA, Chaudhri E, Albrecht JK. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2010; 376: 705-716. PMID: 20692693.
5. Picard O, Cacoub P. Dermatological adverse effects during genotype-1 hepatitis C treatment with the protease inhibitors telaprevir and boceprevir. Patient management. *Clin Res Hepatol Gastroenterol*. 2012; 36: 437-440. PMID: 22483956.
6. Lübbe J. Dermatological side effects. *Hot Topics in Viral Hepatitis*. 2008; 9: 29-35.
7. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009; 361: 580-593. PMID: 19625712.
8. Mistry N, Shapero J, Crawford RI. A review of adverse cutaneous drug reactions resulting from the use of interferon and ribavirin. *Can J Gastroenterol*. 2009; 23: 677-683. PMID: 19826642.
9. Hashimoto Y, Kanto H, Itoh M. Adverse skin reactions due to pegylated interferon alpha 2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus. *J Dermatol*. 2007; 34: 577-582. PMID: 17683392.
10. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011; 364: 2405-2416. PMID: 21696307.
11. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Mullhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M. Telaprevir for retreatment of HCV infection. *N Engl J Med*. 2011; 364: 2417-2428. PMID: 21696308.
12. Roujeau JC, Mockenhaupt M, Tahan SR, Henshaw J, Martin EC, Harding M, van Baelen B, Bengtsson L, Singhal P, Kauffman RS, Stern RS. Telaprevir-related dermatitis. *JAMA Dermatol*. 2013; 149: 152-158. PMID: 23560295.

13. Rosa I. Management of side-effects. *Clin Res Hepatol Gastroenterol*. 2011; 35 Suppl 2: S69-74. PMID: 22248698.

14. Cacoub P, Bourlière M, Lübbe J, Dupin N, Buggisch P, Dusheiko G, Hézode C, Picard O, Pujol R, Segaert S, Thio B, Roujeau JC. Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals. *J Hepatol*. 2012; 56: 455-463. PMID: 21884670.

15. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994; 331: 1272-1285. PMID: 7794310.

16. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int*. 2006; 55: 1-8. PMID: 17075280.

17. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, Roujeau JC. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol*. 2007; 156: 609-611. PMID: 17300272.

18. Hézode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, Poynard T, Samuel D, Bourlière M, Zarski JP, Raabe JJ, Alric L, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Métivier S, Tran A, Serfaty L, Abergel A, Causse X, Di Martino V, Guyader D, Lucidarme D, Grando-Lemaire V, Hillon P, Feray C, Dao T, Cacoub P, Rosa I, Attali P, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol*. 2013; 59: 434-441. PMID: 23669289.

19. Backus LI, Belperio PS, Shahoumian TA, Cheung R, Mole LA. Comparative effectiveness of the hepatitis C virus protease inhibitors boceprevir and telaprevir in a large U.S. cohort. *Aliment Pharmacol Ther*. 2014; 39: 93-103. PMID: 24206566.

20. Bichoupan K, Schwartz JM, Martel-Laferriere V, Giannattasio ER, Marfo K, Odin JA, Liu LU, Schiano TD, Perumalswami P, Bansal M, Gaglio PJ, Kalia H, Dieterich DT, Branch AD, Reinus JF. Effect of fibrosis on adverse events in patients with hepatitis C treated with telaprevir. *Aliment Pharmacol Ther*. 2014; 39: 209-216. PMID: 24266536.

21. Wehmeyer MH, Eißing F, Jordan S, Röder C, Hennigs A, Degen O, Hüfner A, Hertling S, Schmiedel S, Sterneck M, van Lunzen J, Lohse AW, Schulze zur Wiesch J, Lüth S. Safety and efficacy of protease inhibitor based combination therapy in a single-center "real-life" cohort of 110 patients with chronic hepatitis C genotype 1 infection. *BMC Gastroenterol*. 2014; 14: 87. PMID: 24884400.

22. López-Sepúlveda R, Fernández-López C, García Collado C, Jiménez Morales A, Valencia Soto C, Calleja Hernández MÁ. Boceprevir and telaprevir safety in routine clinical practice. *Farm Hosp*. 2014; 38: 44-49. PMID: 24483859.

23. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011; 54: 1433-1444. PMID: 21898493.

24. Dziennik Urzędowy Ministra Zdrowia. Warszawa, dnia 24.04.2013 poz. 17: 623-638.

25. Janczewska-Kazek E, Pisula A, Ścieszka J, Marek.B, Elastography — noninvasive method for assessment of liver fibrosis. *Med Sci Rev*. 2009; 9: 113-116.

26. Biesbroeck LK, Scott JD, Taraska C, Moore E, Falsey RR, Shinohara MM. Direct-acting antiviral-associated dermatitis during chronic hepatitis C virus treatment. *Am J Clin Dermatol*. 2013; 14: 497-502. PMID: 23775427.

27. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; 364: 1207-1217. PMID: 21449784.

28. Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; 364: 1195-1206. PMID: 21449783.

29. Montaudié H, Passeron T, Cardot-Leccia N, Sebbag N, Lacour JP. Drug rash with eosinophilia and systemic symptoms due to telaprevir. *Dermatology*. 2010; 221: 303-305. PMID: 20798484.

30. Hézode C. Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice. *Liver Int*. 2012; 32 Suppl 1: 32-38. PMID: 22212569.

31. Mousa OY, Khalaf R, Shannon RL, Egwim CI, Zela SA, Ankoma-Sey V. Chronic Hepatitis C Therapy in Liver Cirrhosis Complicated by Telaprevir-Induced DRESS. *Case Rep Med*. 2014; 2014: 380424. PMID: 25214847.

32. 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 severe rash. *Hepatology*. 2012; 55: 2042-2043. PMID: 22234749.

33. Kesar V, Kesar V, Khaitova V, Motamed D, Schiano T. Telaprevir-induced DRESS. *J Drugs Dermatol*. 2014; 13: 199-200. PMID: 24509972.

34. Chen ST, Wu PA. Severe cutaneous eruptions on telaprevir. *J Hepatol*. 2012; 57: 470-472. PMID: 22387663.

35. Broccolo F, Ciccarese G, Picciotto A, Drago F. A Case of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Induced by Telaprevir Associated with HHV-6 Active Infection. *J Hepatol*. 2014. pii: S0168-8278(14)00668-0. doi: 10.1016/j.jhep.2014.09.014. PMID: 25239077.

36. Samain A, Duval-Modeste AB, Joly P, Leblanc C, Massy N, Courville P, Goria O, Riachi G. First case of drug rash eosinophilia and systemic symptoms due to boceprevir. *J Hepatol*. 2014; 60: 891-893. PMID: 24333861.

37. Yoneyama K, Miyagishi K, Kiuchi Y, Shibata M, Mitamura K. Risk factors for infections in cirrhotic patients with and without hepatocellular carcinoma. *J Gastroenterol*. 2002; 37: 1028-1034. PMID: 12522534.