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Cutaneous Adverse Events in Patients with Chronic Hepatitis C during Treatment with Directly Acting Antiviral Agents: A cohort study

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ABSTRACT

Background: Hepatitis C virus (HCV) affects approximately 2-2.5% of the global population. In Egypt, the prevalence was reported at 7% in 2015. Over recent years, new direct-acting antiviral (DAA) therapies have been developed. One of the most widely used regimens in Egypt for treating HCV infection is a combination of sofosbuvir and daclatasvir. However, there is still a limited understanding of the potential dermatological side effects associated with these medications.

Objective: This study aimed to evaluate the frequency and clinical manifestations of cutaneous adverse reactions in patients undergoing treatment with direct-acting antiviral drugs.

Patients and methods: This research involved 140 HCV-positive patients who were monitored for 12 weeks during their treatment. Of these, 105 patients were treated with a combination of sofosbuvir and daclatasvir (protocol 1), while 35 patients received the same regimen along with ribavirin (protocol 2). Dermatological evaluations were conducted at the start of treatment and weekly during follow-up visits to identify any skin-related side effects.

Results: Dermatological adverse reactions were observed in 48 patients (34%), with 38 patients (36%) in protocol 1 and 10 patients (28%) in protocol 2. The skin-related issues noted during treatment included itching, mild generalized drug eruptions, hyperpigmentation, dry mouth, acne flare-ups, telogen effluvium, and ecchymosis.

Conclusion: Directly acting antiviral therapy might yield some dermatological adverse effects. Most of them are reversible and don't require stopping of the treatment.

Keywords: Direct acting antivirals, Cutaneous manifestations, Hepatitis C virus, Side effects, Adverse events, viral hepatitis.

INTRODUCTION

Chronic infection with the Hepatitis C virus (HCV) remains a critical global health challenge, affecting approximately 185 million individuals worldwide [1]. In Egypt, HCV and its associated complications represent a substantial public health concern, with particularly high prevalence rates. According to the 2015 demographic survey, 6.3% of the Egyptian population tested positive for HCV antibodies (HCV Abs), with the infection rate progressively increasing with age, peaking at 27.6% in individuals aged 55 to 59 years [2].

In response to this crisis and the predominance of genotype 4, which has proven difficult to treat with interferon-based regimens, Egypt launched a nationwide initiative to combat the HCV epidemic. This program established a network of specialized centers throughout the country, ensuring widespread access to antiviral treatments. HCV infection typically presents without symptoms in its early stages, and extrahepatic manifestations often serve as the initial clues for diagnosis [3].

Among these manifestations, skin disorders constitute a significant comorbidity in HCV patients [4].

Conditions such as mixed cryoglobulinemia (MC), lichen planus (LP), and porphyria cutanea tarda (PCT) are strongly linked to HCV infection. Testing for HCV is recommended in certain dermatological conditions due to their epidemiological and pathogenic association with the virus. Although, psoriasis, chronic pruritus, and necrolytic acral erythema may be related to HCV infection, there is insufficient epidemiological and experimental evidence to support universal HCV screening for these conditions. Additionally, other immune-mediated inflammatory skin disorders, including chronic urticaria and vitiligo, have also been reported in HCV patients [5].

Before 2011, the standard treatment for HCV consisted of pegylated interferon (PEG-IFN) alfa-2a or alfa-2b combined with ribavirin (RBV), though this approach was hampered by extended treatment durations, limited efficacy, and frequent adverse effects [6]. The advent of direct-acting antiviral (DAA) drugs, which specifically target different stages of the HCV life cycle, has made HCV treatment more accessible and tolerable for all patients. DAAs are classified into four groups: NS3/4A protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors [7].

This cohort study aimed to investigate the occurrence and clinical patterns of cutaneous side effects in patients undergoing treatment with direct-acting antivirals for chronic hepatitis C, as more clarity is needed on the dermatological adverse events associated with these medications.

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PATIENTS AND METHODS

This prospective cohort study involved 140 HCV-positive patients who did not present with extrahepatic dermatological symptoms. The sample size was calculated using EPI, with a total of 170 patients receiving treatment at New Cairo Hospital over the past six months. The study excluded 17% of participants who exhibited skin symptoms [8], ultimately including 140 HCV-positive individuals. Patients were recruited between February 2020 and January 2021 from the Dermatology Department of Badr University Hospitals, New Cairo Viral Hepatitis Treatment Center, and the National Liver Institute.

The study participants met the eligibility criteria set forth by the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) guidelines [3].

Inclusion criteria: Individuals aged 18 and older with HCV-related chronic liver disease, confirmed by both anti-HCV antibody and HCV RNA detection.

Exclusion criteria: Patients with Child C cirrhosis and those with platelet counts below 50,000/mm³, as moderate to severe thrombocytopenia often occurs in patients with decompensated liver disease and portal hypertension. Patients with hepatocellular carcinoma were also excluded unless they had undergone curative surgery at least four weeks prior and exhibited no active disease on dynamic imaging (CT, MRI). Patients with extrahepatic malignancies were excluded unless they had been disease-free for two years. Pregnant women, those unable to use effective contraception, patients with poorly controlled diabetes, individuals with systemic diseases displaying dermatological symptoms, patients exhibiting dermatological manifestations of HCV, and those with significant dermatological conditions.

Patients received treatment in accordance with the guidelines established by the National Committee for Control of Viral Hepatitis (NCCVH). HCV-positive individuals were treated with a regimen of sofosbuvir/daclatasvir (SOF/DAC), either without ribavirin (protocol 1) or with ribavirin (protocol 2), for a 12-week duration, followed by an assessment of virological response 12 weeks after the completion of treatment.

All patients were subjected to: Full medical history, thorough dermatological examination including skin, mucous membrane, hair and nails, complete liver biochemical profile (ALT, AST, Bilirubin, Albumin, and P.T.), CBC and FIB -4 was calculated to all patients to evaluate liver state. All participants were tested for HCV by PCR.

Follow-up and dermatological examination of patients was performed monthly during the treatment period and any skin manifestations appearing were documented, photographed and followed up if they persist after the end of treatment.

Ethical considerations: The study was accepted by The Research Ethics Committee, Helwan University (Approval code: REC-FMHU 34-2020). All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The data were analyzed using statistical methods and presented as mean ± standard deviation (SD), 95% confidence intervals (CI), range, or frequencies and percentages, depending on the data type. To assess the normality of numerical data, the Kolmogorov-Smirnov (Shapiro-Wilk) test was applied. Comparisons of numerical variables between the study groups were made using the independent samples Student's t-test, while categorical variables were analyzed using the Chi-square (χ^2) test. In cases where the expected frequency was below five, an exact test was used. The Odds Ratio (OR) along with its 95% Confidence Interval (CI) was calculated for all binary data comparisons between Protocol 1 and Protocol 2. Statistical significance was determined by two-sided p-values less than 0.05. All statistical analyses were carried out using IBM SPSS version 22 (IBM Corp, Armonk, NY, USA) for Microsoft Windows. A two-tailed approach was utilized for all statistical tests, with a significance threshold set at a p-value ≤ 0.05.

RESULTS

One hundred and forty patients completed the study and were included in the analysis. One hundred and 5 patients received protocol 1 (P1) and 35 patients received protocol 2 (P2). The demographic, clinical and laboratory characteristics of the studied patients were listed in table (1). Both groups had matching age and gender with P2 group had significantly longer disease duration, higher viral load and more severe FIB4.

Dermatological adverse events of treatment: Among 140 patients who received HCV therapy, 48 patients (34%) had dermatological adverse events, 38 patients on P1 (36%) compared to 10 patients (28%) on P2. There was no significant association between dermatological adverse events and HCV duration or HCV PCR with p value of 0.316. There were no serious side effects that needed to stop treatment (Table 1 and 2).

Table 1: Demographic, clinical and laboratory characteristics of the two studied groups

	Protocol 1 (n=105)	Protocol 2 (n=35)	P
Age (years)	49.56 ± 13.76	47.97± 13.55	0.538
Gender			
Male	59 (56.2%)	21 (60%)	0.844
Female	46 (43.8%)	14 (40%)	
HCV duration(years)	6.43 ± 2.94	10.14 ± 8.99	<0.001
Interval to Cut. Manifest.	3.24 ± 1.2	3.8 ± 2.57	.316
PLT (x 10^6/L)	275.82 ± 54.23	170.26 ± 29.61	.000
AST (U/L)	32.34 ± 7.98	82.06 ± 13.38	.000
ALT (U/L)	31.03 ±5.78	77.57 ± 4.65	.000
FIB-4	1.18± 0.144	4.38±1.54	.000
HCV PCR	770388.7 ± 14473602.1	3696402.9 ± 1990709.2	.000
Anemia	3 (2.9%)	2 (5.7%)	.599
Drug addiction	1 (1%)	0	.750
Lymphoma	0	1 (2.9%)	.250
Heart disease	0	1 (2.9%)	.250
Epilepsy	0	1 (2.9%)	.250
Diabetic	13 (12.4%)	2 (5.7%)	.221
Hypertensive	8 (7.6%)	1 (2.9%)	.291
Cirrhosis	1 (1%)	5 (14.3%)	.004
Oral hypoglycemic drugs	3 (2.9%)	1 (2.9%)	1
Insulin	9 (8.6%)	1 (2.9%)	.234
Antihypertensive	8 (7.6%)	0	.093
Liver support drugs	2 (1.9%)	7 (20%)	.001
Tamsulin	1 (1%)	0	.750
Inhalers	0	1 (2.9%)	.250
INF	1(1%)	4(11.4%)	0.014
Digoxin	0	1 (2.9%)	.250

HCV: Hepatitis C Virus, PLT: Platelets, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, FIB-4: Fibrosis-4 Index, PCR: Polymerase Chain Reaction, INF: Interferon.

Table 2: Dermatological adverse effects between the two studied groups

	Protocol 1 (n=105)	Protocol 2 (n=35)	$\chi 2$	P		
	Yes	No	Yes	No		
Itching	22 (21%)	83(%79)	4(11.4%)	31(%88.6)	1.57	.158
Rash	2 (1.9%)	103(%98.1)	1 (2.9%)	34(%97.1)	.114	.581
Hyperpigmentation	2 (1.9%)	103(%98.1)	1 (2.9%)	34(%97.1)	.114	.581
Mouth dryness	11 (10.5%)	94(%89.5)	3 (8.6%)	32(%91.4)	.106	.518
Joint stiffness	7 (6.7%)	98(%93.3)	3 (8.6%)	32(%91.4)	.144	.477
Increasing acne & folliculitis	2 (1.9%)	103(%98.1)	1 (2.9%)	34(%97.1)	.114	.581
Hair fall	7 (6.7%)	98(%93.3)	6 (17.1%)	29(%82.9)	3.42	.070
Ecchymosis	0	105(%100)	1 (2.9%)	34(%97.1)	3.02	.250

CASES:

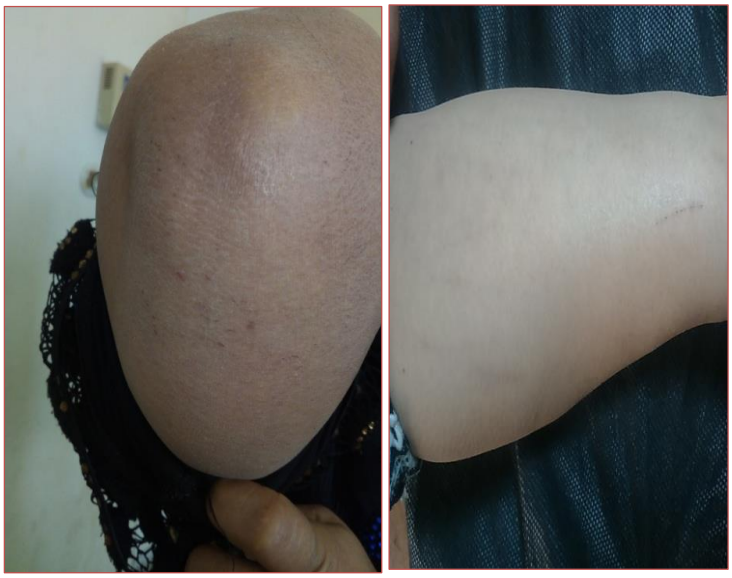

Figure (1): scratch marks of patient during receiving Protocol 1 of HCV treatment

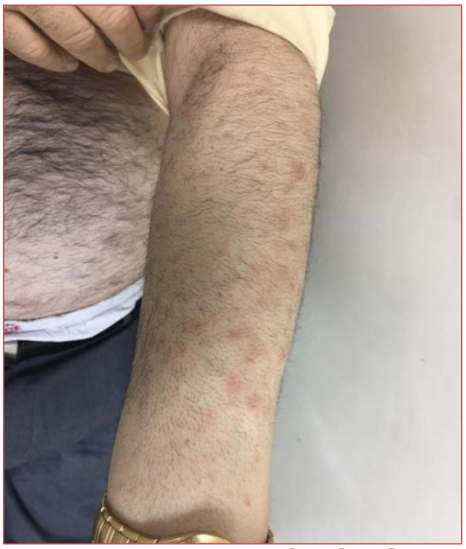

Figure (2): Generalized drug rash appearing during receiving protocol 1 of HCV treatment

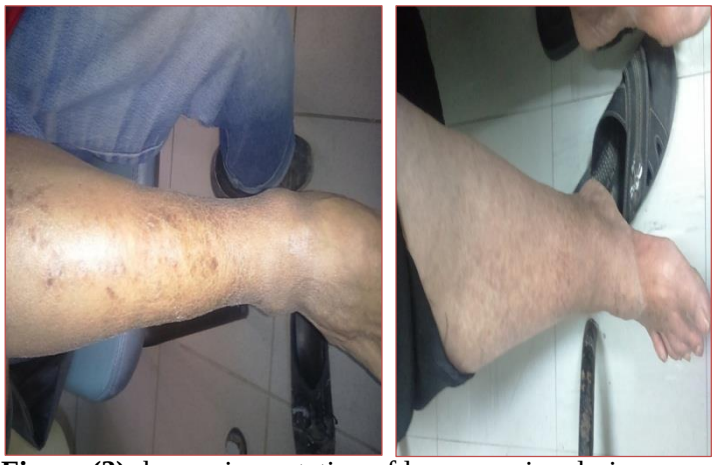

Figure (3): hyperpigmentation of leg appearing during receiving protocol 1 of HCV treatment

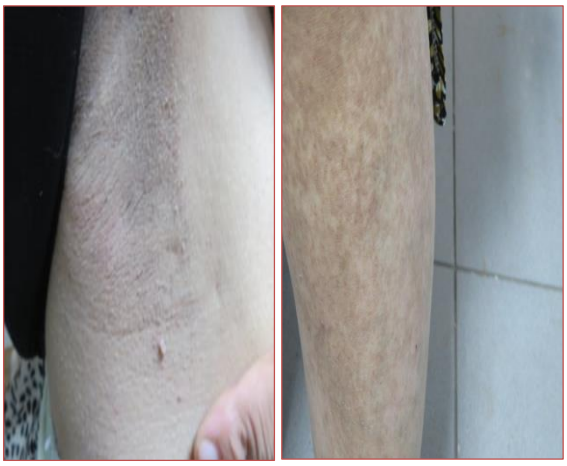

Figure (4): hyperpigmentation appearing under arm and of the leg during receiving protocol 2 of HCV treatment

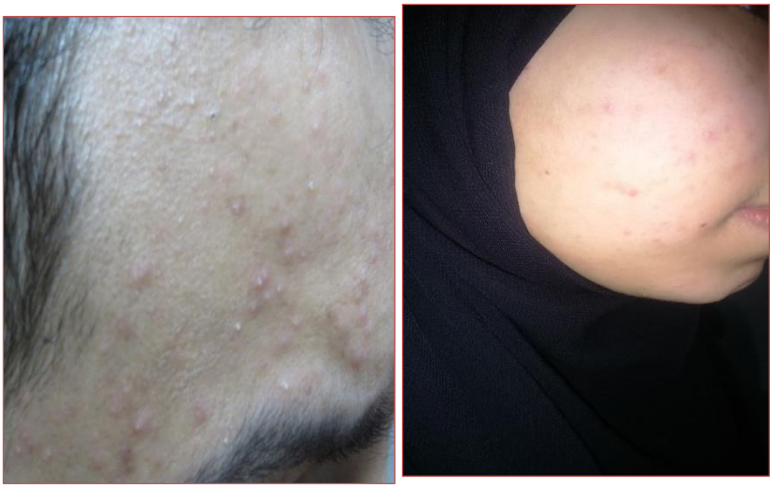

Figure (5): Increasing acne & folliculitis during receiving protocol 1 of HCV treatment

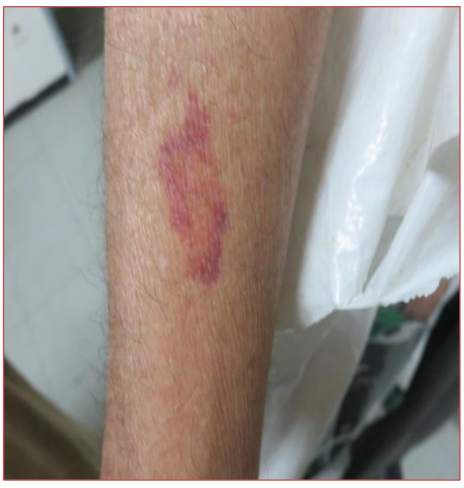

Figure (6): Ecchymosis appearing during receiving protocol 2 of HCV treatment

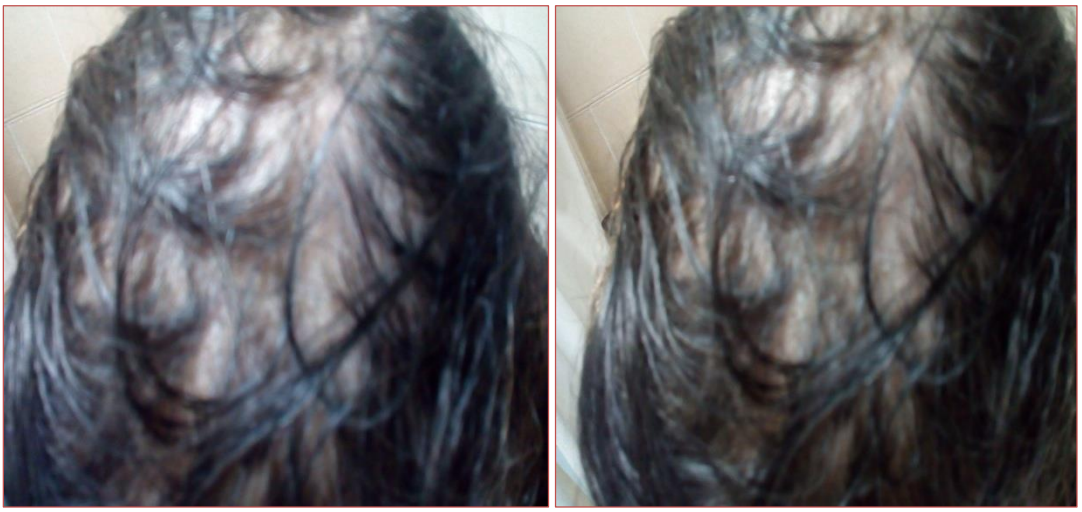

Figure (7): Increasing hair fall of a patient during receiving protocol 1 of HCV treatment.

DISCUSSION

Chronic hepatitis C virus (HCV) infection poses a major public health concern in Egypt, characterized by a high prevalence. The national treatment program has identified the combination of generic sofosbuvir (SOF) and daclatasvir (DCV), with or without ribavirin (RBV), as the primary treatment option due to its cost-effectiveness, achieving a sustained virologic response (SVR) in over 80% of cases [9]. However, cutaneous adverse effects have emerged as a noteworthy issue related to dual and triple antiviral therapies, underscoring the need for efficient detection and management [10].

This hospital-based cohort study included 140 HCV-positive patients who exhibited no extrahepatic dermatological symptoms. Of these, 105 patients were treated with the SOF+DCV regimen (protocol 1), while 35 patients received the same regimen with the addition of ribavirin (protocol 2). A comprehensive dermatological examination, covering the skin, mucous membranes, hair, and nails, was conducted alongside a detailed liver biochemical profile (ALT, AST, bilirubin, albumin, and P.T.), CBC, and FIB-4 score. HCV infection was confirmed in all participants via PCR. Dermatological evaluations and follow-up checks were regularly performed throughout the treatment period, with all skin-related side effects documented, photographed, and monitored post-treatment.

A total of 48 patients (34%) experienced cutaneous side effects, with 38 patients (36%) from protocol 1 and 10 patients (28%) from protocol 2 reporting such events. The recorded dermatological issues included pruritus without visible lesions, leading to scratch marks in 26 patients, generalized mild drug rash in 3 patients, hyperpigmentation in 3 patients, xerostomia (dry mouth) in 4 patients, joint stiffness in 10 patients, flare-ups of pre-existing acne and folliculitis in 3 patients, telogen effluvium in 13 patients, and ecchymosis in 1 patient. The causes of these side effects remain unclear and may be linked to factors such as skin dryness, phototoxic reactions, or neurological changes. Symptoms were often alleviated using topical treatments, antihistamines, and appropriate skincare measures [11].

The immunomodulatory effects of the antiviral drugs, potentially through the pre-hapten/hapten theory, could explain some of these reactions, where drug molecules or their reactive metabolites modify self-proteins, resulting in the formation of neo-antigens [12].

Other possible mechanisms include drug metabolite accumulation in the skin, immune-mediated reactions in genetically predisposed individuals, T-cell-induced damage to keratinocytes, and Fas-mediated apoptosis [13]. A prospective study by **Gaber *et al.*** [14], involving 108 HCV-positive patients confirmed similar findings. In his study, the SOF+DCV+RBV regimen was the most commonly used treatment in 45.4% of patients. Pruritus was the most frequent dermatological side effect, reported in 36.1% of patients, while edema and ecchymosis were among the least common, each affecting 0.9% of patients. Other dermatological manifestations included generalized mild drug rash (17.6%), xerosis (8.3%), oral dryness (1.9%), hyperpigmentation (4.6%), hypopigmentation (1.9%), alopecia (5.6%), oral ulcers (3.7%), joint pigmentation or stiffness (1.9%), photosensitivity (11.1%), and neuropathy (8.3%).

Our analysis did not reveal significant differences in the incidence of skin symptoms based on age, whether patients were above or below 46 years. However, **Roujeau *et al.*** [15] found a higher incidence of treatment-related dermatitis in patients over 45 years of age ($P = 0.03$), possibly due to age-related skin dryness or barrier dysfunction. There was also no significant variation in the timing of dermatological symptoms, whether they occurred during or after treatment. In contrast, **Teixeira *et al.*** [16] reported that 50% of dermatitis cases developed within the first four weeks of therapy, with the remaining 50% occurring by the 12th week, suggesting that rashes may develop at any stage of treatment. The discrepancies in reported side effects may be attributed to underreporting by patients due to the mild nature of the symptoms or other comorbid conditions. No severe or life-threatening side effects were observed in a study by **El-Gammal *et al.*** [17], which involved a similar treatment regimen (SOF+DCV, with

or without RBV). The most frequently reported adverse effects were fatigue, myalgia, headache, and dizziness. The interactions of daclatasvir, a substrate of CYP3A4 and P-glycoprotein, and sofosbuvir, a substrate of the P-glycoprotein transporter, may explain these findings. Co-administration with enzyme inducers or inhibitors of these pathways could result in various side effects [18].

Simpson *et al.* [19] documented two cases of lichenoid eruptions in sun-exposed areas associated with the use of sofosbuvir and simeprevir, which contrasts with our findings. Neither patient received ribavirin, and the eruptions appeared two and four weeks after starting the medication. One patient had a history of vitiligo and allergies to shellfish and ampicillin. Similarly, **Eyre *et al.*** [20] reported a sun-induced skin lesion in an HCV-transplanted patient two weeks after beginning sofosbuvir and simeprevir therapy. After 14 days of topical steroid treatment, the lesions improved, and they resolved completely after the HCV treatment concluded. **Wang *et al.*** [21] presented a case of erythema multiforme triggered by sofosbuvir and daclatasvir in a hepatitis C patient with psoriasis vulgaris and a known allergy to sulfamethoxazole–trimethoprim. These case reports highlight the occurrence of cutaneous reactions caused by direct-acting antivirals (DAAs), particularly in sun-exposed areas and in patients with a history of drug allergies or pre-existing skin conditions before starting HCV treatment. Additionally, those with a history of pharmacodermatitis or skin disorders may be more prone to reactions when ribavirin combinations are used. However, no standardized guidelines exist for preventing severe dermatological reactions in these patients [22].

Study Limitations: The correlation between treatment success and side effects was not evaluated and small numbers of patients in protocol 2 of treatment.

CONCLUSION

Treating HCV with DAAs therapy of HCV had some dermatological adverse effects, most of them were treatable and not severe. The most common adverse events were itching, increasing hair fall, and joint stiffness. There were no significant differences between protocol 1 (ribavirin group) and protocol 2 (non-ribavirin group).

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