A real-life experience of dermatological manifestations associated with direct-acting antivirals for chronic hepatitis C virus infection

Mohamed F. Alsayed[a], Nahed A. Makhlouf[b], Eman R.M. Hofny[c], Hanan M. Nafeh[d], Ahmad F.A. Hasanain[d], Mohamed A. El-Mokhtar[e], Helal F. Hetta[e], Nasr K. Khalil[a], Mohamed A. Mekky[b], Mohamed Alboraie[f], Ahmed M. Nasr[d], Hussein Elamin[g]

[a]Assiut Center for Management of Viral Hepatitis, [b]Department of Tropical Medicine and Gastroenterology, Assiut University, Departments of [c]Dermatology, [d]Tropical Medicine and Gastroenterology, [e]Microbiology and Immunology, Faculty of Medicine, Assiut University, [g]Internal Medicine, Faculty of Medicine, Assiut University and Assiut Center for Management of Viral Hepatitis, Assiut, Egypt, [f]Department of Internal Medicine, Al-Azhar University, Cairo, Egypt

Correspondence to Mohamed F. Alsayed, MSc, Assiut Center for Management of Viral Hepatitis, Assiut 71515, Egypt.
Tel: +20 100 613 7655;
e-mail: dr.mfarouk.git@hotmail.com

Received 16 November 2020
Received 20 November 2020
Accepted 25 November 2020
Published 14 September 2022

Journal of Current Medical Research and Practice
2022, 7:227–231

Background and objectives
Hyperbilirubinemia and photosensitivity reactions are the most common manifestations associated with simeprevir-containing regimens. Simeprevir is photodynamically active as sulfonamide; the absorption of ultraviolet ray may show unwelcome adverse effects.

Aim
We aimed to outline the dermatological manifestations associated with management of chronic hepatitis C infection using direct-acting antivirals.

Patients and methods
This study was carried out on chronic hepatitis C patients receiving sofosbuvir and simeprevir, from February 2015 to February 2016 at Assiut Center for Management of viral hepatitis.

Results
Cutaneous manifestations were observed in 16 (0.8%) patients; 11 (69%) of them were males and five (31%) were females. Photosensitivity reactions were the most common dermatological adverse effects observed; they occurred in 10 (62.5%) out of 16 patients. We diagnosed other dermatological manifestations that were not related to photosensitivity reactions in eight patients, such as erythema and scaling of the scrotum that was diagnosed as scrotal psoriasis. Also, we found furuncles, trophic ulcer, purpuric drug eruption, lichen herpeticus, linear ridges in nails with yellowish and blackish discoloration in lateral nail plate, pityrosporum folliculitis, and pigmentation of the lower lip might be drug-induced or lichen. Sustained virological response 12 was the ultimate fate of all the 16 patients. After the end of therapy, all the dermatological manifestations showed complete resolution.

Conclusion
Treatment with direct-acting antivirals may be associated with dermatological adverse effects that resolve with stopping of therapy.

Keywords:
direct-acting antivirals, hepatitis C virus, mucocutaneous toxicity, photosensitivity, simeprevir

J Curr Med Res Pract 7:227–231

2357-0121

Introduction

Hyperbilirubinemia and photosensitivity reactions are the most common manifestations associated with simeprevir-containing regimens [1,2]. Simeprevir is photodynamically active; the absorption of ultraviolet ray may show unwelcome adverse effects [3]. The photosensitivity reactions were observed during administration of simeprevir and their severity increases in a dose-dependent way [4,5]. Even in patients using sun-block measures, photosensitivity reactions can develop, and patients may need to stop simeprevir temporarily or permanently [6]. The reported manifestations of photosensitivity reactions of simeprevir suggest the development of phototoxicity rather than photoallergy [5]. However, up till now, how simeprevir exactly precipitates photosensitivity reactions is still not clear [7].

Aim

To report the occurrence of any dermatological adverse effects associated with simeprevir/sofosbuvir combination therapy in chronic hepatitis C (CHC) Egyptian patients.

Patients and methods

This observational study aimed to outline the dermatological manifestations associated with simeprevir/sofosbuvir combination therapy used

in treating Egyptian patients with CHC virus infection in a real-life experience. The study population was 2040 Egyptian patients with CHC virus infection (genotype 4) who received a combination therapy of sofosbuvir (400 mg/day) and simeprevir (150 mg/day), from February 2015 to February 2016. All patients were advised to avoid sun exposure and to put sun-block creams before sun exposure and also to cover sun-exposed areas if possible. Cases who developed dermatological symptoms after receiving simeprevir/sofosbuvir combination therapy, were further examined by consultant of dermatology to report these lesions and to determine whether these lesions are due to drug side effects or not.

Inclusion criteria

(1) Patients with CHC virus infection having confirmed positive HCV RNA.
(2) Age range: 18–70 years.
(3) Agreement to use contraception or stopping sexual activity for women of childbearing potential or men with a female partner of childbearing potential must agree to use an effective form of contraception.

Exclusion criteria

(1) Liver cirrhosis child B and C. Patients with hepatocellular carcinoma, except after successful intervention.
(2) Liver disease not related to chronic HCV infection.
(3) Previous treatment with direct-acting antivirals (DAAs). Co-infection with HIV. Total serum bilirubin more than or equal to 3 mg/dl. Serum albumin less than 2.8 g/dl. Internationa normalized ratio more than or equal to 1.7.
(4) Platelet count less than 50 000/mm^3. Serum creatinine above 2.5 mg/dl.
(5) Extrahepatic malignancy, except after 2 years of stoppage of disease-free interval.

Ethical issues

The current study was carried out after the approval of the Clinical Research Ethical Committee of Assiut Faculty of Medicine was taken, and it was conducted according to the code of ethics of the World Medical Association (Declaration of Helsinki). All participants accepted using their photos and signed a consent certificate after discussing in detail the certificate subjects and the study aim. Participants were informed that refusal of participating in the study will not affect having the full benefit of the optimum medical service. Data confidentiality was respected.

Statistical analysis

Data were collected and entered into Excel software program and further analyzed by SPSS Software Package (IBM SPSS version 24, USA), Version 23, frequency and percent were used to describe qualitative data, and mean/SD was used to describe quantitative data. For statistical analyses and presentation of the results, differences between categorical variables were assessed by χ^2 test. Continuous variables were compared using the Student's t test or Mann–Whitney test as appropriate.

Results

The study included 2040 Egyptian patients with chronic HCV infection (genotype 4) who received a combination therapy of sofosbuvir (400 mg/day) and simeprevir (150 mg/day) during a 1-year period. Baseline

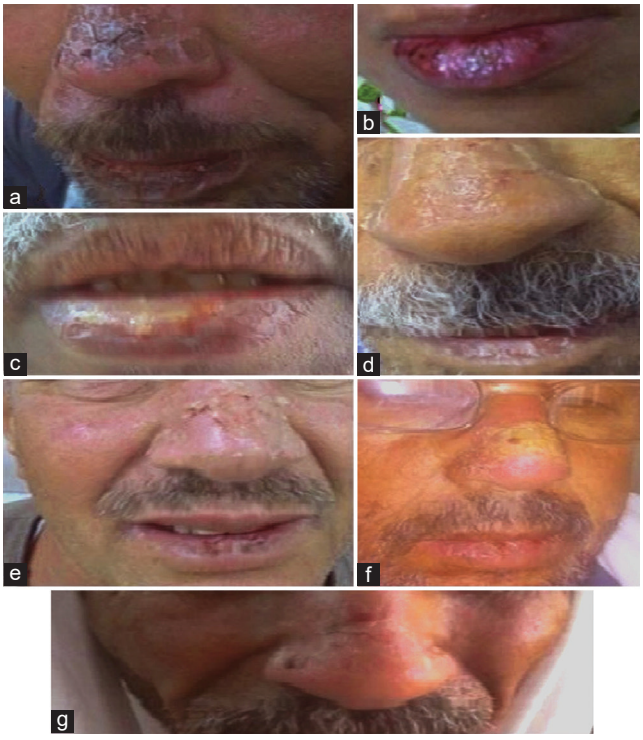
Table 1 Demographic data, treatment status, fibrosis stage, and baseline laboratory data of the study group

Variables	Patients with the dermatological side effects (*n*=16)	Patients without the dermatological side effects (*n*=2024)
Sex		
Male	11 (69)	1394 (69.42)
Female	5 (31)	614 (30.57)
Age (years)		
Mean±(SD)	51.85±7.80	53.21±6.89
Minimum–maximum	35-65	30-67
Fibrosis stage by Fibroscan		
F0	2 (12.5)	262 (12.94)
F1	3 (18.7)	385 (19.01)
F2	4 (25)	492 (24.31)
F3	5 (31.3)	726 (35.86)
F4	2 (12.5)	159 (7.88)
Liver stiffness by Fibroscan (kPsc)		
Mean±SD	9.57±7.3	9.35±7.82
Median	8.8	8.3
Minimum–maximum	4-25.3	4.3-43
Diabetes		
Yes	3 (18.7)	360 (17.78)
No	13 (81.3)	1664 (82.21)
Treatment status		
Naive	14 (87.5)	1727 (85.32)
INF-experienced	2 (12.5)	281 (13.88)
BMI	26.41±4.8	27.25±3.89
Prothrombin conc. (%)	92.21±7.3	93.07±8.14
Albumin (g/dl)	4.2±0.4	4.85±0.5
Alfa-fetoprotein (IU/ml)	5.3±3.2	5.66±0.3
Bilirubin (mg/dl)		
Mean±SD	0.7±0.5	0.82±0.4
Median	0.9	1
Minimum–maximum	0.5-1.8	0.4-1.9
Leukocytic count (K/cmm)	5.3±0.7	5.21±0.54

Data were expressed as number and percentage or mean±SD.
INF, interferon.

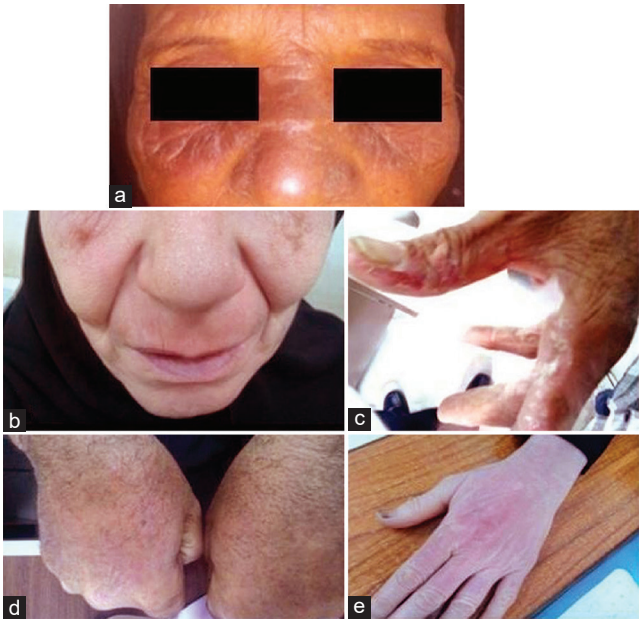
data of the study group are shown in Table 1; the majority were male (61%). Associated diabetes mellitus was found in 27% of cases. The majority were treatment-naive (89%). Cutaneous manifestations were observed in 16 (0.8%) patients; 11 (69%) of them were males and five (31%) were females, as shown in Table 1. Photosensitivity reactions were the most common dermatological adverse effects observed, they occurred in 10 (62.5%) out of 16 patients. Sustained virological response (SVR12) was the ultimate fate of all the 16 (100%) patients. Some patients had more than one type of skin lesions. As shown in Fig. 1a–g, the main dermatological manifestations that forced our study patients to seek medical advice were photosensitivity reactions noticed in their lower lip and nose (sun-exposed areas) in seven patients. Fig. 2a–e shows photosensitivity reactions in faces and hands (sun-exposed areas) of four patients. Unexpectedly, we diagnosed few other dermatological manifestations that were not related to photosensitivity reactions in eight patients among the 16 study patients. As shown in Fig. 3a–j, we found erythema and scaling of the scrotum that was diagnosed as scrotal psoriasis; also, we found furuncles in two patients, trophic ulcer, purpuric drug eruption, lichen herpeticus, linear ridges in nails with yellowish and blackish discoloration in lateral nail plate, pityrosporum folliculitis, and pigmentation of the lower lip might be drug-induced or lichen. All the dermatological manifestations were observed during the initial 4 weeks of therapy, except macules and papules that were detected in a patient's leg during the 12th week of treatment (Fig. 3d). None of these manifestations led to the stoppage of treatment, except (patient 8) with periorbital erythema, edema, and scaling (Fig. 2a) that was advised to stop the DAA drugs for 1 week. Patients with photosensitivity reactions were treated by advising them never to be sun-exposed and stressed to use sun block for skin areas not affected and also to use oral antihistaminic drugs to overcome itching. In cases where more erosions occurred due to scratching, local antibiotics and corticosteroids were prescribed. All other lesions were managed accordingly, either by oral antihistaminic if there is itching or a local antibiotic if it was indicated. Lesions that did not cause itching and without any erosions left without any drug therapy and just the same precautions of sun-block usage and avoiding sun exposure. After the completion of simeprevir/sofosbuvir therapy, all the dermatological manifestations gradually disappeared with complete resolution with no residual sequelae as shown in Fig. 4a, b. There were two patients (patients 13 and 14) who dropped out from dermatological follow-up after achieving SVR12; till that time, they showed partial improvement of their lesions. Before starting simeprevir/sofosbuvir combination therapy, the difference between the two groups (those who developed and those who

Figure 1



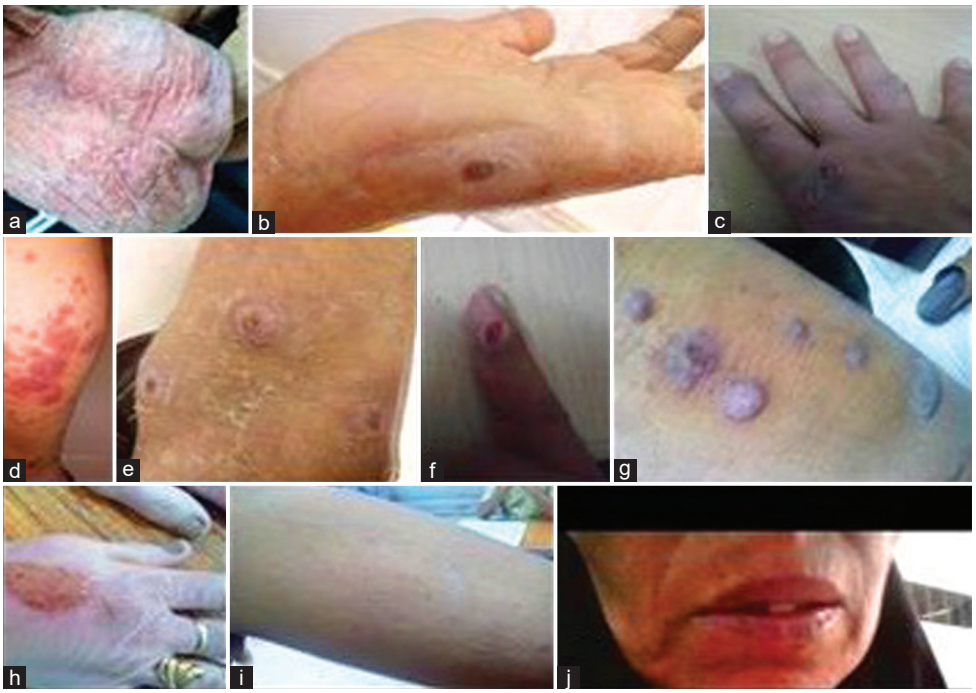
Photosensitivity reactions in the lower lip and nose. (a) Patient 1: lower lip: solar cheilitis, nose: erythema, scaling, and crustation, and photosensitivity dermatitis. (b) Patient 2: lower lip: erythema, edema, and erosions. (c) Patient 3: lower lip: pigmentation and erosions, solar cheilitis. (d) Patient 4: nose: photosensitivity, lower lip: solar cheilitis. (e) Patient 5: lower lip: crustation, nose: erythema, photosensitivity, and solar cheilitis. (f) Patient 6: nose: erythema, scaling, and yellowish crustation, lip: erythema, scaling, crustation, photosensitivity dermatitis, and solar cheilitis. (g) Patient 7: nose: scaling and erosions, photosensitivity dermatitis.

Figure 2



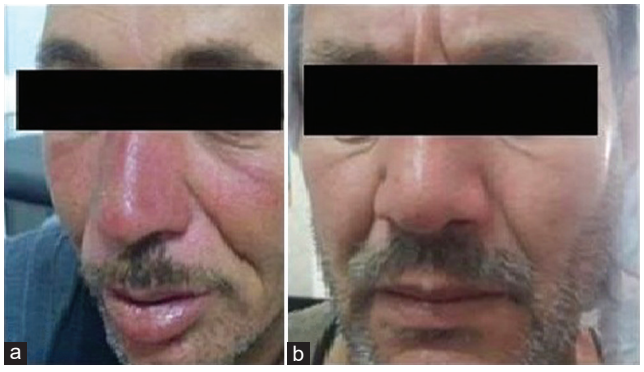
Photosensitivity reactions in the face and hands. (a) Patient 8: face: periorbital erythema, edema, and scaling. (b) Patient 9: erythema and scaling, photosensitivity dermatitis. (c) Patient 7: hand: erythematous scaly plaques over sides of the fingers. (d) Patient 1: hand: papular lesions and erythematous scales, photosensitivity dermatitis. (e) Patient 9: hand: erythema, edema, and peeling photosensitivity.

Figure 3



Dermatological side effects due to drug-induced toxicity rather than photosensitivity. (a) Patient 10: scrotum: erythema and scaling. (b) Patient 11: hand: ulcers on the medial side of the palm, mostly 'healing bacterial infection fruncules'. (c) Patient 12: hand of the diabetic patient: erythema and desquamation, mostly healed bacterial infection 'furuncles' at dorsum of the hand and side of the ring finger. (d) Patient 13: leg: macules, papules, and patchy iris-like lesions. (e) Patient 11: leg: ulcers on the extensor surface of the leg, mostly healing bacterial infection 'furuncles.' (f) Patient 12: hand middle finger: clean ulcer in a diabetic patient, mostly trophic ulcer. (g) Patient 14: right leg: pigmentation and hypertrophic plaques over extensor aspect of the leg. (h) Patient 9: hand: erosions as a result of itching, peeling nails: linear ridges, yellowish discoloration, and blackish discoloration in lateral nail plate. (i) Patient 15: upper arm: erythematous popular lesions. (j) Patient 16: lower lip: pigmentation.

Figure 4



Complete resolution of dermatological manifestations after the completion of simeprevir/sofosbuvir therapy. (a) Patient 1: posttreatment with SMV/SOF. (b) Patient 5: posttreatment with SMV/SOF.

did not develop the dermatological side effect) is of no statistical significance, regarding age, sex, BMI, treatment status, diabetes status, total leukocytic count, serum bilirubin, serum albumin, prothrombin, alfa fetoprotein, viral load, and fibrosis stage [Table 1].

Discussion

In registry-based studies, about 17% of HCV patients present at least one skin manifestation, which can be directly or indirectly induced by chronic HCV infection [8]. Dermatologists should be ready to treat these patients with HCV-related cutaneous manifestations [9]. Cutaneous adverse effects associated with DAAs may be aggravated by combination therapies due to synergism between the coadministered dugs [10]. In a study made by Garcovich *et al.* [11], the percentage of cutaneous adverse effects was 0.8%. The presence of cutaneous adverse effects in the new regimens remains an issue that needs to be addressed, especially in the case of simeprevir, with an incidence of discontinuation due to cutaneous adverse effects of 1.2% [11].

Also, Simpson *et al.* [12] found that photosensitivity was more common with simeprevir (4%) group than placebo (0.8%) group. In the present study, we observed cutaneous manifestations in 16 (0.8%) patients: 11 (69%) of them were males and five (31%) were females. Photosensitivity reactions were the most common dermatological adverse effect observed, they occurred in 10 (62.5%) out of 16 patients. Solar chelitis was manifested in seven (43.8%) patients. There were furuncles in the hands of two patients (patients 11 and 12) and actually this is difficult to be explained or to be referred to the drug. Fig. 3a–j shows dermatological manifestations that are not related to photosensitivity reactions; this may suggest that the dermatological

side effects of simeprevir are considered drug-induced toxicity rather than photoallergy or photosensitivity.

The complete resolution of the all dermatological manifestations gradually with no residual sequelae confirms that the problem is not really serious if we gave a proper psychological and medical support to the affected patients, and to persuade them to complete their course of simeprevir therapy. Due to achieving SVR12 in all the 16 patients with dermatological side effects, we can consider that appearance of dermatological side effects during treatment with simeprevir/sofosbuvir combination, may be a predictor of successful clearance of the virus.

In this study, increased noticed cases of dermatological side effects caused by simeprevir/sofosbuvir combination may be partially related to increased sun's ultraviolet rays in Upper Egypt.

Conclusion

The present study highlights the dermatological adverse effects associated with the new DAAs. We hope then that physicians would be more aware with these adverse effects while treating chronic HCV patients with DAA combinations. During daily real-life practice, good monitoring, optimum treatment, and patient awareness are needed to decrease dermatological adverse effects beside achieving HCV cure.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Reference

1 Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I, *et al.* Once-daily simeprevir (TMC435) with pegylated interferon and ribavirinin treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. Hepatology 2013; 58:1918–1929.

2 Manns M, Marcellin P, Poordad F, *et al.* Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, doubleblind, placebo-controlled phase 3 trial. Lancet 2014; 384:414–426.

3 Storck H. Photoallergy and photosensitivity: due to systemically administered drugs. Arch Dermatol 1965; 91:469–482.

4 Gaetano JN. Benefit–risk assessment of new and emerging treatments for hepatitis C: focus on simeprevir and sofosbuvir. Drug Healthc Patient Saf 2014; 6:37.

5 Mullard A. 2014 FDA drug approvals. Nat Rev Drug Discov 2015; 14:77–81.

6 Banerjee D, Reddy KR. Safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. Aliment Pharmacol Ther 2016; 43:674–696.

7 Moore DE. Drug-induced cutaneous photosensitivity. Drug Saf 2002; 25:345–372.

8 Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C related Child's class A cirrhosis. Gastroenterology 2015; 148:762–770.

9 Wiznia LE, Laird ME, Franks JrAG. Hepatitis C virus and its cutaneous manifestations: treatment in the direct-acting antiviral era. J Eur Acad Dermatol Venereol 2017; 31:1260–1270.

10 Chung RT, Davis GL, Jensen DM, *et al.* Hepatitis C guidance: AASLD-IDSA HCV Guidance Panel recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62:932–954.

11 Garcovich S, Garcovich M, Capizzi R, *et al.* Cutaneous manifestations of hepatitis C in the era of new antiviral agents. World J Hepatol 2015; 7:2740.

12 Simpson CL, McCausland D, Chu EY. Photo-distributed lichenoid eruption secondary to direct anti-viral therapy for hepatitis C. J Cutan Pathol 2015; 42:769–773.