Anti-Nuclear Cytoplasmic Antibody–Associated Vasculitis: A Probable Adverse Effect of Sofosbuvir Treatment in Chronic Hepatitis C Patients

Youssef K. Ahmad^{}; Salwa Tawfeek[†]; Mohamed Sharaf-Eldin[‡]; Hassan E. Elbatea[§]; Abdelrahman Kobtan[‡]; Ferial El-Kalla[‡]; Rehab Badawi[‡]; and Sherief Abd-Elsalam^{*}*

ABSTRACT

Background: Egypt has the largest hepatitis C virus (HCV) epidemic worldwide. Sofosbuvir is an antiviral drug acting by inhibition of the HCV NS5B polymerase. It has shown high efficacy in combination with several other drugs and has a low reported rate of side effects.

Objective: The aim of this prospective cohort study was to assess the safety of sofosbuvir-based treatment regimens used to treat chronic hepatitis C infections and to detect any side effects of sofosbuvir not previously reported.

Methods: We studied treatment side effects in 3,000 patients with chronic HCV infection treated with sofosbuvir and ribavirin for 24 weeks or treated by pegylated interferon, sofosbuvir, and ribavirin triple therapy for 12 weeks. The endpoint of the study was the end of treatment.

Results: Hyperbilirubinemia occurred frequently during treatment in both groups. Treatment was discontinued in 72 cases due to hepatic decompensation and drug complications; 8 of the cases had deep vein thrombosis (DVT) and 7 had cerebral ischemia. Surprisingly, 177/3,000 (5.9%) patients presented with abnormal bleeding, 85 of whom had a vasculitic skin rash.

Conclusion: We report the occurrence of previously nonrecorded side effects with sofosbuvir, namely DVT and bleeding disorders associated with anti-nuclear cytoplasmic antibody (ANCA)–associated vasculitis (AAV). We believe this to be the first report of sofosbuvir-induced AAV skin lesions and bleeding disorders.

Key Words—HCV, interferon, sofosbuvir, vasculitis

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Egypt is the country with the largest hepatitis C virus (HCV) epidemic worldwide.¹ The genotype distribution in Egypt is mainly genotype 4, which is responsible for more than 90% of the infections, with the remaining due to HCV genotype 1.²

Until 2011, the combination of pegylated interferon (Peg-INF) and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C.³ With this regimen, patients infected with HCV genotype 1 had sustained virologic response (SVR) rates of approximately 40% to 50%. Higher SVR rates were achieved in patients infected with HCV genotypes

2, 3, 5, and 6 (around 80%), and intermediate SVR rates (43%-70%) were achieved in those with HCV genotype 4.^{4,5}

New HCV directly acting antivirals (DAAs), namely sofosbuvir, simeprevir, daclatasvir, and ledipasvir, were licensed in Europe in 2014 for use in combination therapies for HCV infection. Sofosbuvir, a pangenotypic nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase, was approved in January 2014.⁶ Sofosbuvir is a highly potent inhibitor of the HCV NS5B polymerase that has shown high efficacy in combination with several

*Al-Azhar University, Department of General Medicine; [†]National Research Center, Department of Internal Medicine; [‡]Tanta University, Department of Tropical Medicine and Infectious Diseases, Tanta, Egypt; [§]Kafr El-Sheikh University, Department of Tropical Medicine and Infectious Diseases. Corresponding author: Sherief Abd-Elsalam, Tropical Medicine Department, Tanta University Hospital, El Geish Street, Tanta, Gharbia Governorate, Egypt; e-mail: Sherif_tropical@yahoo.com.

other drugs, with and without Peg-INF, against HCV. It offers many advantages; it is an orally administered drug with high potency, a reportedly low rate of side effects, and a high barrier to resistance (requires a greater number of critical mutations to render treatment ineffective).⁷

Patients infected with HCV genotype 4 can be treated with a combination of weekly Peg-INF- α , daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily sofosbuvir (400 mg) for 12 weeks. The sustained viral response (SVR) rate reported for this regimen by the Neutrino study was 96%.⁸

According to the European Association for the Study of the Liver (EASL) 2014 guidelines, patients infected with HCV genotype 4 who are IFN intolerant or ineligible can be treated with daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or $\geq$ 75 kg, respectively) and daily sofosbuvir (400 mg) for 24 weeks.⁹

Common side effects of sofosbuvir include fatigue, headache, nausea, insomnia, itching, anemia, weakness, rash, decreased appetite, chills, flu-like illness, fever, diarrhea, joint pain, and irritability as reported in the *Sovaldi* (sofosbuvir) tablets product monograph.¹⁰ The present prospective cohort study was performed to assess the safety of sofosbuvir-based treatment regimens used to treat chronic HCV infection and to detect any previously unreported side effects of sofosbuvir.

PATIENTS AND METHODS

This is a prospective cohort study of 3,000 patients with naïve or IFN-experienced chronic HCV infection attending the El-Ebor clinic from January 1, 2015 to September 20, 2015. HCV was diagnosed by positive HCV polymerase chain reaction (PCR). All patients were tested for fasting blood sugar (FBS), serum creatinine, complete blood count (CBC), and liver function tests as shown in Table 1. Testing for HBs-Ag, α -fetoprotein, thyroid-stimulating hormone (TSH), and antinuclear antibody (ANA) and abdominal ultrasonography, electrocardiogram (ECG), and fundal eye examination were performed for all patients before starting treatment.

Patients were classified into 2 groups. Group 1 included 1,200 patients, ineligible for IFN therapy, who received dual therapy with one sofosbuvir 400 mg tablet daily plus oral weight-based ribavirin (1,000 mg/day for those weighing <75 kg or 1,200 mg/day for those weighing $\geq$ 75 kg) for 24 weeks. Group 2 included 1,800 patients, eligible for IFN therapy, who

received triple therapy with one 400 mg sofosbuvir tablet daily plus oral weight-based ribavirin (as with the dual therapy) and a 180 mcg Peg-INF alpha 2a subcutaneous injection weekly for 12 weeks.

Criteria for IFN eligibility were age 18 to 60 years old, serum bilirubin $\leq$ 1.2 mg/dL, serum albumin $\geq$ 3.5 mg/dL, prothrombin activity $\geq$ 75%, total leucocytic count $\geq$ 4,000/mm³, absolute neutrophil count $\geq$ 1,500/mm³, platelet count $\geq$ 150,000/mm³, hemoglobin concentration $\geq$ 13 g/dL for males and 12 g/dL for females, ANA $\leq$ 2-fold normal, absence of proliferative retinopathy, esophageal or gastric varices, current autoimmune diseases including thyroid diseases, and no history of organ transplantation.

Patients with a Child-Pugh score of >7, platelets <50,000, renal failure, HCC (hepatocellular carcinoma) except 4 weeks after successful intervention, extra hepatic malignancies except after a 2-year disease-free interval, and pregnant females were excluded from the study.

Liver fibrosis was assessed by liver biopsy or fibroscan, and the METAVIR staging system was used for grading activity and staging fibrosis.¹¹ Liver function was assessed using the Modified Child-Pugh score.¹² All patients receiving triple therapy had liver fibrosis F1 or F2 with Child-Pugh score 5. Patients receiving dual therapy had liver fibrosis F3 or F4 with Child-Pugh score 6 or 7. None of the patients had a history of bleeding disorders. All unnecessary medication was stopped, and the patients were advised not to take any over-the-counter medications or supplements during the treatment period.

Follow-up of patients in group 1 was performed every month during treatment when the patients attended the clinic to receive their monthly prescriptions. The patients were asked if they had experienced any side effects and were clinically evaluated. CBC and liver and kidney function tests were performed every month. PCR for HCV was performed after 1, 3, and 6 months of treatment. Follow-up of patients in group 2 was performed on a weekly basis when the patients came to the clinic to be given their weekly Peg-INF injections. CBC and liver and renal function tests were performed after 1, 2, 4, 8, and 12 weeks of treatment, whereas PCR was performed after 4 and 12 weeks of treatment in addition to clinical evaluation for side effects of treatment every week. In the present study, clinical evaluation was recorded at any time throughout the study, while laboratory investigations were reported after 3 months of treatment. The endpoint of the study was the end of HCV treatment.

Testing for P-anti-neutrophil cytoplasmic antibodies (ANCA) and C-ANCA was performed in 150/177 cases with bleeding disorders (60 on dual therapy and 90 on triple therapy) and in 30 patients without bleeding disorders (the other patients refused investigations).

Skin biopsies were taken from 50 patients with skin rash (20 from group 1 and 30 from group 2) for histopathological examination to assess degree of vessel wall damage, to detect extravascular hemosiderin deposition, and to evaluate presence and type of cellular infiltrate.

Data were expressed as mean $\pm$ SD. Differences between groups were tested with 2-tailed Student's *t* test for unpaired data. For correlation analysis, Pearson's correlation coefficient was calculated. A value of $p \leq 0.05$ and a value of $r \geq 0.05$ were considered significant.

RESULTS

In the present study, hemoglobin concentrations decreased significantly during treatment in both groups. This decrease was more pronounced in group 1 than in group 2; the hemoglobin dropped in group 1 from 12.5 ± 1.5 to 9.8 ± 1.3 g/dL ($p < 0.01$), whereas it dropped in group 2 from 14.8 ± 1.0 to 12.5 ± 1.2 g/dL ($p < 0.05$). WBC and platelet counts were not affected in group 1 but significantly decreased in group 2 ($p < 0.01$). During treatment, serum bilirubin

levels rose significantly in both groups, but more so in patients from group 2. Bilirubin rose from $0.8 \pm .01$ to $4.1 \pm .03$ mg/dL ($p < 0.01$) in group 2 and rose from $1.2 \pm .02$ to 3.5 ± 1.2 mg/dL ($p < 0.05$) in group 1. There was a highly significant rise in liver enzymes in patients from group 2 ($p < 0.01$) as well as a significant rise among patients from group 1 ($p < 0.05$). Serum creatinine, FBS, serum albumin, and PT were not affected in both groups (Table 1).

In the present study, the incidence of fatigue, myalgia, headache, fever, loss of appetite, neutropenia, and thrombocytopenia was significantly higher in group 2 than group 1 ($p < 0.01$ for all), however the incidence of anemia was significantly higher in group 1 than group 2 ($p < 0.05$). On the other hand, there were no significant changes between the 2 groups regarding insomnia, pruritus, asthenia, rash, irritability, influenza-like illness, nausea and vomiting, diarrhea, and bleeding disorders (Table 2).

We recorded the occurrence of thrombotic disorders in the form of cerebral ischemia in 7 patients (0.23%) and deep vein thrombosis (DVT) in 8 patients (0.26%). Cerebral ischemia occurred in 6 (0.5%) patients from group 1 and 4 (0.3%) from group 2. DVT occurred during treatment in 2 patients (0.11%) from group 1 and 3 patients (0.16%) from group 2 (Table 3). Treatment was discontinued for these patients.

The overall incidence of bleeding disorders during treatment in our study was 5.9%. These occurred in 85 patients (7%) from group 1 and in 92 patients

Table 1. Baseline laboratory and end of treatment investigations for all patients

	Group 1 (<i>n</i> = 1,200)			Group 2 (<i>n</i> = 1,800)		
	Before treatment	End of treatment	<i>p</i>	Before treatment	End of treatment	<i>p</i>
Hemoglobin, g/dL	12.5 ± 1.5	9.8 ± 1.3	$<0.0001^{**}$	14.8 ± 1.0	12.5 ± 1.2	$<0.05^*$
WBC/mm ³	3.9 ± 1.5	3.8 ± 1.2	NS	5.8 ± 1.2	3.1 ± 2.3	$<0.0001^{**}$
Platelets $\times 10^3$ /mm ³	129 ± 8	115 ± 12	NS	210 ± 24	150 ± 50.2	$<0.0001^{**}$
Creatinine, mg/dL	0.9 ± 0.2	0.92 ± 0.3	NS	0.85 ± 0.12	0.84 ± 0.2	NS
Fasting blood glucose, mg/dL	115 ± 10	116 ± 9	NS	114 ± 6	113 ± 5	NS
ALT, IU/L	62 ± 15	120 ± 22	$<0.05^*$	32 ± 5	120 ± 12	$<0.0001^{**}$
AST, IU/L	68 ± 16	128 ± 23	$<0.05^*$	35 ± 6	130 ± 15	$<0.0001^{**}$
Bilirubin, mg/dL	$1.2 \pm .02$	3.5 ± 1.2	$<0.05^*$	$0.8 \pm .01$	$4.1 \pm .03$	$<0.0001^{**}$
Albumin, mg/dL	$3.8 \pm .05$	$3.2 \pm .02$	NS	4.6 ± 1.4	4.4 ± 1.2	NS
Prothrombin concentration, %	76 ± 3	78 ± 4	NS	96 ± 4	90 ± 6	NS

Note: NS = nonsignificant. ALT = alanine aminotransferase; AST = aspartate aminotransferase; NS = nonsignificant; WBC = white blood cells. * $p < 0.05$, significant. ** $p < 0.01$, highly significant.

Table 2. Incidence of drug side effects during first 3 months of treatment

Items	Group 1 (<i>n</i> = 1,200)	Group 2 (<i>n</i> = 1,800)	<i>p</i>
	<i>n</i> (%)	<i>n</i> (%)	
Fatigue	438 (36.5)	987 (54.8)	<0.0001**
Myalgia	313 (26.1)	878 (48.8)	<0.0001**
Headache	323 (26.9)	711 (39.5)	<0.0001**
Fever	298 (24.8)	1213 (67.4)	<0.0001**
Insomnia	167 (13.9)	311 (17.3)	NS
Pruritus	118 (9.8)	197 (10.9)	NS
Asthenia	96 (8)	184 (10.2)	NS
Rash	93 (7.8)	157 (8.7)	NS
Loss of appetite	43 (3.6)	199 (11.1)	<0.0001**
Diarrhea, nausea, and vomiting	72 (6)	113 (6.3)	NS
Irritability	32 (2.8)	53 (2.9)	NS
Influenza-like illness	85 (7.1)	713 (39.6)	<0.0001**
Anemia	125 (10.4)	150 (8.3)	<0.05*
Neutropenia	13 (1.1)	212 (11.8)	<0.0001**
Thrombocytopenia	17 (1.4)	178 (9.9)	<0.0001**
Incidence of bleeding disorders	85 (7)	92 (5)	NS

Note: NS = nonsignificant.

p* < 0.5, significant. *p* < 0.01, highly significant.

(5%) from group 2. The bleeding disorders were in the form of epistaxis, bleeding gums, menorrhagia, and vasculitic skin lesions (Table 4). The most common bleeding disorder in both groups was the occurrence of vasculitic skin lesions in the form of palpable purpura, areas of hyperpigmentation, necrosis, and

Table 3. Thrombotic disorders during first 3 months of treatment

Thrombotic disorders	Total (<i>n</i> = 3,000)	Group 1 (<i>n</i> = 1,200)	Group 2 (<i>n</i> = 1,800)
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Deep vein thrombosis	8 (0.26)	6 (0.5)	2 (0.11)
Cerebral ischemia	7 (0.23)	4 (0.3)	3 (0.16)

Table 4. Bleeding disorders during first 3 months of treatment

Total no. of patients with bleeding disorders: 177/3,000 (5.9%)	Group 1 (85/1,200) (7%)	Group 2 (92/1,800) (5%)
Epistaxis	24/85	39/92
Bleeding gums	18/85	12/92
Menorrhagia	12/85	6/92
Vasculitic skin lesions	40/85	45/92

ulceration in 85 patients (Figure 1). All of the patients presenting with bleeding disorders were found to have within normal blood platelet counts, PT, and serum creatinine and no albuminuria. Patients with epistaxis, bleeding gums, and skin lesions did not need specific treatment and completed their course of treatment; the lesions resolved spontaneously after the end of treatment.

Skin biopsies were taken from 50 patients with skin lesions (20 from group 1 and 30 from group 2), and leucocytoclastic infiltration was detected in 95% and 90% of the cases from groups 1 and 2, respectively (Table 5) (Figure 2). Most patients with vasculitic skin lesions tested positive for ANCA leading to a diagnosis of ANCA-associated vasculitis (AAV).

Figure 1. Leukocytoclastic skin infiltrations.**Table 5.** Results of skin biopsy

	Group 1	Group 2
No. of patients with biopsy taken from skin lesions	20	30
No. of patients with leukocytoclastic infiltration	19/20 (95%)	27/30 (90%)

Figure 2. Sofosbuvir induced skin lesion with some necrotic and scarred areas. Hyperpigmentation at the ankle and dorsum of the foot that correspond to areas of vasculitis.

ANCA was positive in 54/60 patients (90%) on dual therapy and in 78/90 patients (87%) with triple therapy (no significance differences between them); the overall incidence of ANCA positivity in patients with bleeding disorders was 88% (Table 6).

Treatment was discontinued for 67 patients in group 1 due to the appearance of complications precluding continuation of treatment: These were hepatic decompensation in the form of hepatic encephalopathy with markedly elevated bilirubin in 22 cases and development of ascites in 35 cases. Treatment was also stopped for 6 cases with DVT and 4 cases with cerebral ischemia; all these patients had F4 stage of liver fibrosis and Child-Pugh score ≥ 6 . In group 2, treatment was discontinued for only 5 cases: 2 with DVT and 3 with cerebral ischemia.

HCV RNA was undetectable by quantitative PCR at the end of treatment for all participating patients who continued the treatment.

DISCUSSION

HCV infection has led to a major global health problem that requires widespread active interventions for its prevention and control.¹³ In 2011, Egypt was described as having the highest prevalence rate of HCV in the world.¹⁴ Many of those infected may ultimately progress to advanced liver disease and/or hepatocellular cancer. However, those outcomes can be prevented by treatment, which is rapidly improving and offers the potential of a cure to more patients than has been previously possible. The primary goal of HCV therapy is to cure the infection.¹³

The Egyptian government has been facing important challenges, including raising the awareness of the population about infection and transmission, strengthening infection control measures, and providing treatment to those in need.¹⁵ The Ministry of Health in Egypt has embarked on a national treatment program for patients with chronic HCV infection since 2006. Annually, 40,000 to 50,000 patients have been treated.¹⁶

IFN and ribavirin combination therapy for chronic HCV produces a number of well-described side effects, in particular influenza-like symptoms (fever, myalgia, and rigors), several gastrointestinal disturbances (nausea, diarrhea, and weight loss), and depression. Injection site reactions and injection site inflammation are particularly common, although it is noted that these are generally mild and rarely dose limiting.¹⁷ Uncommon serious adverse events are retinopathy, retinal hemorrhage,¹⁸ visual loss, tinnitus, hearing loss, cardiac arrhythmias, congestive heart failure, interstitial pneumonitis, acute renal failure, bacterial infections (particularly in patients with

Table 6. ANCA study in our subjects

	Group 1	Group 2	
No. of patients for whom ANCA was studied	60 patients with bleeding disorders	90 patients with bleeding disorders	30 patients without bleeding disorders from both groups
No of patients with positive ANCA	54/60 (90%)*	78/90 (87%)*	3/30 (10%)
Total percentage	88%	10%	

Note: Anti-nuclear cytoplasmic antibody (ANCA).

* $p < 0.01$, highly significant.

cirrhosis), induction or exacerbation of autoimmune diseases, hyperthyroidism, hypothyroidism, acute psychosis, panic attacks, and severe depression.¹⁹ Premature withdrawal from therapy due to adverse events was necessitated in 10% to 14% of participants in registration trials of these agents. Most adverse events were safely and effectively managed by dose reduction using predetermined criteria. The most common indications for dose reduction were hematologic abnormalities, such as anemia and neutropenia, with the latter being more frequent in Peg-IFN treatment arms. Recent data suggest that maintaining adherence to a prescribed treatment regimen can enhance antiviral response.²⁰

In the present study, hemoglobin concentrations decreased significantly during treatment in both groups. This is to be expected as it is well known that ribavirin treatment is commonly associated with anemia. Ribavirin exerts its toxicity through an inhibition of intracellular energy metabolism and oxidative membrane damage, leading to an accelerated extravascular hemolysis by the reticulo-endothelial system.²¹ Anemia was more prominent during treatment in group 1 than group 2; this can be explained by the lower pretreatment hemoglobin levels in group 1 and that most patients in group 1 had compensated cirrhosis (F3-F4).

In the present study, the incidence and type of side effects in the 2 groups were similar to those previously reported.^{10,17-20} However we report occurrence of bleeding incidents in 5.9% of our cases, with no statistical difference in incidence between the patients from group 1 and the patients in group 2 receiving IFN in spite of normal prothrombin activity and platelet count in this category of patients.

Bleeding disorders in the form of epistaxis, bleeding gums, menorrhagia, and vasculitic skin rash were present in patients treated with sofosbuvir and ribavirin with or without IFN, and they were not reported by the treatment-experienced patients when they were previously treated with IFN and ribavirin without sofosbuvir. This raises the suspicion that the bleeding tendency may be related to sofosbuvir. To our knowledge, this side effect has not been reported by any previous studies to date.

Eighty-five of the 177 cases (48%) with bleeding disorders in both groups had vasculitic skin lesions in the form of palpable purpura, areas of hyperpigmentation, necrosis, and ulceration. Histopathology reports on biopsies taken from the skin lesions revealed leukocytoclastic infiltration in 19/20 (95%) cases from group 1 and 27/30 (90%) from group 2,

which corresponds to vascular damage caused by nuclear debris from infiltrating neutrophils.²²

Drug-induced vasculitis represents approximately 10% of acute cutaneous vasculitis cases.²³ It is often a diagnosis made after exclusion of other causes for cutaneous vasculitis, such as infection or autoimmune disease.²⁴

It is known that HCV is a commonly recognized cause of leucocytoclastic vasculitis, likely through the presence of cryoglobulins,²⁵ yet none of our patients had experienced the appearance of these skin lesions prior to inclusion to the study and taking sofosbuvir.

We have found only one case report by Dautriche et al²⁶ of cutaneous leucocytoclastic vasculitis occurring in a chronic HCV patient treated with sofosbuvir and daclatasvir.

ANCA test was positive in 88% of our patients who developed bleeding disorders and in 10% of those who did not. There was no statistically significant difference between those from groups 1 or 2, yet there was a highly significant difference between those who experienced bleeding incidents and those who did not. Most of the patients with vasculitic skin lesions tested positive for ANCA, leading to a diagnosis of AAV.

ANCA are important serological markers for certain small-vessel vasculitis, encompassing Wegener granulomatosis (WG), microscopic polyangiitis (MPA), and Churg–Strauss syndrome (CSS). ANCAs are classified by the indirect immunofluorescence (IIF) technique into P-ANCAs, which have a perinuclear pattern, and C-ANCAs, which evince a cytoplasmic pattern. Evidence is mounting that these specific antibodies are pathogenic in small-vessel vasculitis,^{27,28} yet the etiology of AAV is still largely unknown.

In our study, the clinical manifestations of AAV were mild without renal involvement and all manifestations resolved spontaneously after cessation of treatment, consolidating our assumption that the condition was drug induced. From data of retrospective studies of AAV, the overall prognosis is much better than that of primary AAV. The mortality rate and the frequency of developing end-stage renal disease is lower, and no relapse of vasculitis occurs during long-term follow-up after discontinuation of the offending drugs.²⁹ The possible reasons of good prognosis in patients with drug-induced AAV include the mild clinical manifestations and less crescents in renal histopathology at presentation,³⁰ discontinuation of the causal drug substantially reduces the drug-associated immune response, and ANCA has low avidity and absence of the IgG3 subclass.³¹

We speculate that sofosbuvir may induce AAV. Assessment with the Naranjo algorithm indicated that this was a probable adverse reaction to the drug.³² There is no mention of this side effect in the manufacturer's product monograph, however a recent publication³³ has reported a case of ANCA crescentic allograft glomerulonephritis following sofosbuvir administration in a kidney transplant recipient. We found no mention of cutaneous AAV due to sofosbuvir treatment in the literature and therefore believe that this is the first report of sofosbuvir-induced cutaneous AAV.

We recorded the occurrence of thrombotic disorders in the form of cerebral ischemia in 7 patients (0.23%) and DVT in 8 patients (0.26%). Cerebral ischemia has been recorded in a study by Doss et al in 2015.³⁴

Our study is limited by our inability to observe recurrence of the condition on re-administration of the drug, inability to introduce a control group in which a placebo was administered, and testing for effect of increasing or decreasing the drug dose on severity of the reaction. These limitations were due to ethical considerations.

CONCLUSION

This study records the occurrence of bleeding disorders in 177/3,000 patients (5.9%) receiving sofosbuvir for treatment of chronic HCV. Eighty-five (48%) of the cases with bleeding disorders had vasculitic skin lesions, which were diagnosed as AAV. To our knowledge, this is the first report of sofosbuvir-induced AAV skin lesions and bleeding disorders. We also recorded occurrence of thrombotic disorders in the form of DVT in 8/3,000 patients (0.26%) and cerebral ischemia in 7/3,000 patients (0.23%) patients receiving sofosbuvir.

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The study protocol was approved by the ethical committee of faculty of medicine, Tanta University. Informed consent was obtained from each patient before participation in the study.

The authors report no conflicts of interest.

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