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The effects of directly acting antiviral-related sustained virological response on the risk of extrahepatic manifestations of hepatitis C infection

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Summary

Background: Direct-acting antiviral (DAA) therapy may have a beneficial role in extrahepatic manifestations of hepatitis C virus (HCV) infection. However, the available data are limited.

Aims: To examine the effect of DAA treatment on the risk of several extrahepatic manifestations of HCV.

Methods: We conducted a retrospective cohort study of patients from the US Department of Veterans Affairs Corporate Data Warehouse who had a positive HCV RNA test and received first course of DAAs between 2012 and 2016. We calculated incidence rates by sustained virological response (SVR) status for 6 extrahepatic manifestations, and effect of SVR on these conditions was evaluated in adjusted Cox regression models.

Results: Of the 45,260 patients treated with DAA with mean follow-up of 2.01 years, 41,711 (92.2%) experienced SVR. Incidence rates ranged from 0.17/1000 PY for porphyria cutanea tarda to 21.04/1000 PY for diabetes in the SVR group and 0.51/1000 PY for porphyria cutanea tarda to 23.11/1000 PY for diabetes in the no SVR group. The risk was reduced with SVR for mixed cryoglobulinemia (adjusted HR (aHR)= 0.23 ; 95% CI 0.10-0.56), glomerulonephritis (aHR=0.61; 95% CI 0.41-0.90), and lichen planus (aHR=0.46; 95% CI 0.30-0.70), but not for non-Hodgkin's lymphoma (aHR=0.86; 95% CI 0.52-1.43) or diabetes (aHR=0.98; 95% CI 0.81-1.19). Non significant risk reduction was seen for porphyria cutanea tarda (aHR=0.33; 95% CI 0.11-1.03).

Conclusions: Successful DAA treatment resulting in SVR was associated with significant reductions in the risk of mixed cryoglobulinemia, glomerulonephritis, lichen planus, and possibly porphyria cutanea tarda but not non-Hodgkin lymphoma or diabetes.

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Hepatitis C virus (HCV) infection affects approximately 185 million individuals around the world. HCV infection leads to chronic hepatitis, cirrhosis and hepatocellular carcinoma. Chronic HCV infection is also associated with several extrahepatic manifestations, including essential mixed cryoglobulinemia, some subtypes of B-cell non-Hodgkin lymphoma (NHL), membranoproliferative glomerulonephritis, porphyria cutanea tarda and lichen planus.¹ There is also consistent epidemiological evidence supporting the association of chronic HCV infection with type- 2 diabetes mellitus. These conditions have been associated with added morbidity and cost.²

HCV antiviral therapy with attainment of sustained virological response (SVR), which is virological cure, has hepatic benefits, such as normalizing liver enzymes, halting the progression of liver disease, and reducing the risk of hepatocellular carcinoma. Studies in the interferon-based treatment era showed that SVR was also associated with a reduced risk of mixed cryoglobulinemia; glomerulonephritis; porphyria cutanea tarda; NHL³; and, possibly, diabetes mellitus.⁴⁻⁷

With the introduction and increased use of direct-acting antivirals (DAA) that have much better efficacy in achieving SVR than interferon-containing regimens, we expect a reduction in the risk of some extrahepatic manifestations of chronic HCV infection. These benefits could be important enough to be included in the cost-benefit analyses for overall HCV treatment. However, apart from case reports and case series, there only few systematic studies on the effect of DAA-related SVR on extrahepatic manifestations.⁸ We, therefore, conducted the largest to-date retrospective cohort study of HCV-infected patients to evaluate the effect of DAA-induced SVR on the risk of extrahepatic manifestations.

METHODS

The US Department of Veterans Affairs (VA) operates the largest medical system in the United States with 153 medical centers, 745 community-based outpatient clinics, and several other supportive-care facilities grouped into 21 Veterans Integrated Service Networks throughout the United States. The VA Corporate Data Warehouse was our primary study data source. Corporate Data Warehouse data exist on the VA Informatics and Computing Infrastructure platform in a relational database. It includes all lab test results and pharmacy data, as well as inpatient and outpatient utilization in the form of International Classification of Diseases, Ninth and Tenth Editions (ICD-9 and 10) (from October 2015) diagnoses codes and Vital Status.

Study Population

We identified a study cohort of patients with active HCV and treated with DAAs, by applying the following inclusion criteria: (1) at least 1 positive serum HCV RNA or genotype test from October 1, 1999, to December 30, 2016; (2) at least 18 years at the time of the HCV index date; (3) DAA treatment without simultaneous interferon, defined by sofosbuvir, simeprevir, ledipasvir/sofosbuvir, dasabuvir/ombitasvir/paritaprevir/ritonavir, daclatasvir, or elbasvir/grazoprevir with or without ribavirin received from any VA nationwide pharmacy with courses beginning between September 1, 2012, to July 1, 2016; and (4) had lab testing required to verify SVR status. The date of the first DAA prescription

was considered as the DAA index date, and extrahepatic manifestation outcomes data were evaluated through November 1, 2017, the end of the study period. This allowed *at least* 1 year of follow-up after treatment completion and SVR status was ascertained to determine the presence of extrahepatic conditions. We examined only the first course of DAA treatment; subsequent DAA courses were not considered.

We defined SVR by undetectable HCV RNA in all follow-up HCV RNA tests at least 4 weeks after the end of treatment (SVR4). We chose SVR4 because of its high correlation with SVR12 in previous studies.⁹ If there was at least 1 positive HCV RNA result any time posttreatment, we classified the patient as not achieving SVR. Those with unknown SVR status because of a lack of RNA testing were excluded from all analyses. Prior HCV treatment experience was defined as filled prescription of interferon-based regimen with or without ribavirin, or first-generation DAA (i.e., boceprevir, telaprevir) prior to index date.

The outcomes of interest were mixed cryoglobulinemia, glomerulonephritis, lichen planus, porphyria cutanea tarda, NHL and diabetes, each defined by having at least 1 inpatient or outpatient ICD-9/10 diagnosis. Diabetes was defined as 2 or more outpatient or 1 or more inpatient codes, or at least 1 VA prescription for oral hypoglycemic drugs or insulin. Patients were identified as having a prevalent case if the ICD-9/10 code of extrahepatic manifestations was present any time before or 6 months after the DAA index date. Incident cases were defined as those occurring at least 6 months (i.e., specifically, 26.07 weeks) after DAA index date after exclusion of patients with prevalent extrahepatic conditions. All patients were followed-up until their last visit to a VA medical facility, death, or November 1, 2017.

Potential confounders defined in the cohort included age at the DAA index date, gender, race/ethnicity, HCV genotype (as separate binary variables indicating a history of type 1a, 1b, 2, 3, 4, and 5 or 6), healthcare utilization and comorbidities. The VA utilization variable is defined as the number of outpatient visits to a VA medical facility within 1 year before and 1 year after DAA index date as separate binary variables (high and low), indicating greater and lower than the median number of visits. Other covariates included history of alcohol and/or drug abuse, hypertension, hepatitis B virus (HBV), HIV co-infection, and cirrhosis and its complications (ascites, variceal bleeding, hepatic encephalopathy or hepatorenal syndrome) any time before the DAA index date based on inpatient or outpatient ICD-9/10 diagnoses codes. Diagnoses codes used to define these conditions were obtained from the Agency for Healthcare Research and Quality Clinical Classifications Software (Supplementary Table).

Data Analysis

We examined the effects of SVR following DAA treatment on risk of developing extrahepatic manifestations in HCV+ patients. The outcomes were incident cases diagnosed during follow-up, as defined above. We calculated the incidence rates by dividing number of outcomes by total person-years by SVR status for each condition as well as incidence rate ratios (IRR) and their corresponding 95% confidence intervals (CI), using unconditional maximum likelihood and normal approximation. We determined whether attainment of SVR after DAA affects the risk of extrahepatic manifestation outcomes, as measured by the

incidence of these outcomes. We fitted multivariable Cox proportional hazards regression models with HCV treatment having 2 levels –treated with SVR, and treated without SVR. We performed unadjusted, minimally adjusted and fully adjusted models. Minimally adjusted models included age, sex, and race/ethnicity; and fully adjusted models included these variables in addition to preexisting alcohol abuse, drug abuse, HIV, hypertension, cirrhosis, cirrhosis complications, HBV, pre- and postutilization data, HCV treatment experience, and HCV genotype.

We conducted two sensitivity analyses to test the robustness of our results. First, we redefined the outcomes of interest using a more specific definition of two outpatient or one inpatient diagnosis codes. Second, we restricted the analysis to patients who had data available to determine SVR12 as this definition is used more frequently in clinical trials.

An alpha of 0.05 was used as the criteria for statistical significance. All statistical analyses were conducted using R version 3.5.1.¹⁰

RESULTS

We identified 46,930 patients with active HCV infection who received DAA, fulfilled the eligibility criteria. They were mostly men (96.63%), and their racial/ethnic distribution was 53.78% white and 37.27% black (Table 1). The mean age was 61.77 years (SD: 6.54) at DAA treatment index date. SVR was detected in 92.16% of those treated with DAAs. The mean duration for follow-up after DAA index date for the cohort was 2.01 years (median: 1.99 years; SD: 1.78). The types of DAA medications used were sofosbuvir with or without ledipasvir (34103, 81.76%), ombitasvir/paritaprevir/ritonavir (6192, 14.85%), elbasvir/grazoprevir (1018, 2.44%), simeprevir (2609, 6.25%), and daclatasvir (669, 1.60%).

There were no major differences in age, sex, race or duration of follow-up between the 2 groups of patients with SVR and without SVR following DAA treatment. There were also no significant differences between the SVR and no-SVR group in coinfection with HIV or HBV, or hypertension (Table 1). However, the no-SVR group had significantly greater proportions of patients with cirrhosis and history of alcohol or drug abuse; and HCV genotypes non-1a or 1b than the SVR group. Patients without SVR also had greater healthcare utilization both before and after DAA treatment.

The prevalence of extrahepatic manifestations is shown in Table 2. The prevalence of 1 or more of these 5 conditions (all except diabetes) was 7.09% overall [7.05% in SVR vs. 7.61% in no-SVR ($p = 0.2234$)] and 35.46% overall if including diabetes [35.14% in SVR vs. 39.22% in no-SVR ($p < 0.0001$)]. The overall incidence rates of potential extrahepatic manifestations stratified by SVR status are shown in Table 2. The incidence rates (and IRR) of all the extrahepatic manifestation outcomes were quantitatively lower among those who achieved SVR vs. those who did not achieve SVR and were statistically significantly lower for mixed cryoglobulinemia (IRR=0.25; 95% CI 0.10–0.59), glomerulonephritis (IRR=0.58; 95% CI 0.39–0.86), porphyria cutanea tarda (IRR= 0.32; 95% CI 0.11–0.98), and lichen planus (IRR= 0.47 ; 95% CI 0.31–0.71) in the SVR than the non-SVR group.

The unadjusted, minimally adjusted (age, sex and race) and fully adjusted (age, sex, race, alcohol abuse, drug abuse, HIV, hypertension, cirrhosis, cirrhosis complications, HBV, pre- and postutilization, prior non-DAA treatment for HCV, and HCV genotype) proportional hazards for each condition are shown in Table 2. Extrahepatic manifestation risk was reduced in the SVR group compared with the group treated but with no SVR for mixed cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, and lichen planus in the unadjusted and minimally adjusted analyses. The model adjustments did not change appreciably the magnitude, significance or direction of the protective associations for mixed cryoglobulinemia (adjusted HR (aHR)=0.23; 95% CI 0.10–0.56; p=0.0012), glomerulonephritis (aHR=0.61; 95% CI 0.41–0.90; p=0.0126), and lichen planus (aHR=0.46; 95% CI 0.30–0.70; p=0.0003).. SVR was associated with a reduction in risk of porphyria cutanea tarda, but it was only marginally statistically significant in the fully adjusted model (aHR=0.33; 95% CI 0.11–1.03; p=0.057) likely due to a small number of outcomes (n=4) among those without SVR. SVR was not associated with a significant reduction in the risk of non-Hodgkin's lymphoma or diabetes. We found comparable results to the main analysis for both sensitivity analyses (i.e. using more specific outcome definition and using SVR12; Supplementary Tables 1 & 2).

DISCUSSION

We estimated the risk of developing several possible HCV-related extrahepatic manifestations in a large cohort of DAA-treated patients and analyzed the effect of SVR on the extrahepatic condition risk. We found that successful DAA treatment resulting in SVR was associated with significant reductions in the future risk of several conditions, including mixed cryoglobulinemia, glomerulonephritis and lichen planus but not NHL or diabetes. The magnitude of risk reductions ranged between 0.23 and 0.61; and the findings were robust for several adjustments for potential confounders, including several demographic and clinical variables, additional risk factors for these extrahepatic manifestations and healthcare utilization. There was risk reduction in porphyria cutanea tarda; but, even in our large cohort, the incidence of porphyria cutanea tarda was too low to allow for a suitably powered statistical analysis.

Our study is the first to address the possible effect of DAA-related SVR on the risk of developing new cases of extrahepatic manifestation rather than resolution of existing ones. The findings highlight the causal role of active HCV in these conditions and the role of DAA-related SVR as a preventive measure. The findings also support growing literature about successful DAA treatment and resolution of mixed cryoglobulinemia vasculitis with^{11, 12} or without renal¹³ involvement with minimum side-effects,¹⁴ and a mechanism related to changes in peripheral B- and T-cell homeostasis.¹⁵ A previous study with a similar design conducted using national VA data among patients receiving interferon-based HCV therapy reported risk reductions when patients with SVR were compared with treated patients without SVR for mixed cryoglobulinaemia, glomerulonephritis, porphyria cutanea tarda and diabetes but not NHL.⁴

We did not show statistically significant reduction in the incidence of porphyria cutanea tarda, NHL or diabetes in the DAA-related SVR group compared to the DAA treated, no-

SVR group. Studies have consistently shown both strong association between HCV and porphyria cutanea tarda and resolution of porphyria cutanea tarda, with successful HCV treatment including DAAs.^{16, 17} However, in our study the incidence of new porphyria cutanea tarda cases in the SVR group was 19 (4 in the no-SVR group); and, although the difference in the numbers is clear and in favor of SVR, it was not statistically significant due to low power. Diabetes has been variably associated with active HCV infection,¹⁸ and some but not all reports indicate a possible improvement in glycemic control and HgbA1c and decreased insulin use¹⁹ following DAA-related SVR.^{20–22} However, the attributable fraction to HCV is small; and, therefore, the expected reduction in diabetes risk with SVR is expectedly very small. The link between chronic HCV infection and a subset of B-cell NHL is strongly supported by epidemiological studies.²³ Peginterferon/ribavirin therapy has proved its crucial role in the cure of these NHLs; and DAA-related SVR has been associated with a favorable response among patients with B-cell lymphoproliferative disorders, including NHLs²⁴ and possibly marginal zone lymphoma.^{25, 26} However, B-NHL is a heterogeneous group of lymphomas with varied clinical presentation and may be indolent or aggressive. Antiviral treatment may be sufficient for low-grade lymphomas, but chemotherapy is necessary in patients with high-grade lymphomas.²⁷

The results of this study should be considered in the context of several limitations. First, since this is an observational study, selection bias is possible. However, the study was limited to those who received DAA treatment, thus minimizing the possible differences between the SVR and non-SVR groups. Also, we only examined the first course of DAA treatment. This may have resulted in some patients who were in the no SVR group eventually having an SVR; however, since our follow-up time was relatively short we expect this occurrence only in few people with minimal effect on the results. Second, patients with a shorter duration of follow-up time are less likely to obtain incident diagnoses; and this is independent of their SVR status but an artifact of the length of follow-up in the database. However, the duration of follow-up was/was not appreciably different by SVR status. Third, some of the incident extrahepatic manifestation diagnoses may represent prevalent or preexisting cases; but this misclassification is likely to be similar among the SVR and no-SVR groups. Furthermore, all risk estimates were adjusted for healthcare utilization, as measured by the number of outpatient visits, a surrogate measure of the likelihood of making new diagnoses. Fourth, our definition for the extrahepatic manifestations might have low specificity and falsely identified additional patients with the conditions of interest; therefore, we created a more restrictive specific definition and found comparable results. In addition, our SVR4 definition may have over identified patients with SVR; therefore, we conducted a sensitivity analysis using SVR12 and found comparable results. Finally, our results may not be generalizable outside the VA healthcare system as our cohort was overwhelmingly male, older, and lower socioeconomic status than HCV patients outside the VA system.

In addition to its unique focus on the preventive effect of DAA on extrahepatic manifestations, our study has several other strengths. The large sample size coupled with moderately long duration of follow-up (average 2 years) allowed capture of sufficient outcome events in both those with and without SVR to allow a meaningful analysis of most conditions of interest. The study also uses accurate, lab test-based definitions of HCV

infection and SVR, as well as DAA treatment, based on pharmacy records. The observed overall SVR of 92.1% is consistent with effectiveness data for DAA in community-based studies and further adds to the internal validity of the results.^{28, 29}

The study also provides unique estimates of the prevalence and incidence of several possible extrahepatic manifestations in patients with HCV, stratified by SVR status. The prevalence of these extrahepatic conditions in this study is 7.09% and 35.46% if diabetes is considered. The risk attributable to HCV in these conditions is unclear but is likely to be high in porphyria cutanea tarda; low in diabetes; and intermediate for NHL, lichen planus and glomerulonephritis. Successful DAA treatment resulting in SVR was associated with significant reductions in the risk of several conditions, including mixed cryoglobulinemia; glomerulonephritis lichen planus; and, possibly, porphyria cutanea tarda but not non-Hodgkin lymphoma or diabetes. These data should be considered when discussing overall burden of HCV disease and cost effectiveness of screening and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations, in order of appearance:

HCV	hepatitis C virus
DAA	direct-acting antiviral
SVR	sustained virological response
NHL	non-Hodgins lymphoma
VA	Department of Veterans Affairs
ICD	International Classification of Diseases
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
aHR	adjusted hazard ratio

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Table 1:

Demographic and clinical characteristics of 45,260 patients with HCV by SVR status.

	SVR N=41,711	No SVR N=3,549	p-value
Mean age (SD)	61.8	61.41	0.0006
Mean follow-up time, yrs (SD)	2.01	2.07	0.0002
Sex			
Female	1449 (3.47)	76 (2.14)	<0.0001
Male	40262 (96.53)	3473 (97.86)	
Race/Ethnicity			
White	22453 (53.83)	1886 (53.14)	0.0001
Black	15585 (37.36)	1285 (36.21)	
Hispanic	1745 (4.18)	210 (5.92)	
Others	911 (2.18)	80 (2.25)	
Missing	1017 (2.44)	88 (2.48)	
Alcohol Abuse	22052 (52.87)	2021 (56.95)	<0.0001
Drug Abuse	20817 (49.91)	1889 (53.23)	0.0002
HIV Co-infection	1717 (4.12)	135 (3.80)	0.39
Hypertension	30800 (73.84)	2631 (74.13)	0.7186
Cirrhosis	12516 (30.01)	1438 (40.52)	<0.0001
Cirrhosis Complications	7137 (17.11)	981 (27.64)	<0.0001
HBV Co-infection	1285 (3.08)	126 (3.55)	0.13
Pre DAA-High Utilization	20508 (49.17)	1915 (53.96)	<0.0001
Post DAA-High Utilization	19971 (47.88)	2009 (56.61)	<0.0001
Previous HCV Treatment			
None	33769 (80.96)	2841 (80.05)	0.0005
Interferon + Boceprevir/telaprevir	1598 (3.83)	103 (2.90)	

	SVR	No SVR	p-value
	N=41,711	N=3,549	
Interferon +/- ribavirin	6344 (15.21)	605 (17.05)	
HCV Genotype			
Genotype 1a	24097 (57.77)	2039 (57.45)	0.72
Genotype 1b	11371 (27.26)	697 (19.64)	<0.0001
Genotype 2	3664 (8.78)	418 (11.78)	<0.0001
Genotype 3	1901 (4.56)	404 (11.38)	<0.0001
Genotype 4	397 (0.95)	33 (0.93)	0.97
Genotype 5,6	28 (0.07)	5 (0.14)	0.22

Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response; SD, standard deviation; HBV, hepatitis B virus; DAA, direct acting antivirals. All Ns prior to exclusion for prevalent outcomes. P-values are based on t-tests for continuous variables and chi-square for categorical variables.

Table 2:

Prevalence, crude incidence rates, and Cox proportional hazard models (univariate and multivariate) comparing risk of EHM conditions in DAA treated patients with and without SVR

Outcome	SVR			No SVR			Unadjusted		Minimally Adjusted*		Fully Adjusted**	
	Prev/100	Events	IR/1000 PY	Prev/100	Events	IR/1000 PY	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Mixed cryoglobulinemia	1.09	20	0.22	1.1	7	0.9	0.24 (0.10-0.58)	0.0013	0.24 (0.10-0.56)	0.0011	0.23 (0.10-0.56)	0.0012
Glomerulonephritis	2.55	195	2.21	2.68	29	3.8	0.58 (0.39-0.85)	0.0055	0.57 (0.38-0.84)	0.0044	0.61 (0.41-0.90)	0.0126
Porphyria cutanea tarda	1.09	15	0.17	1.13	4	0.51	0.33 (0.11-0.99)	0.0482	0.33 (0.11-1.00)	0.0492	0.33 (0.11-1.03)	0.06
Lichen planus	1.43	141	1.58	1.52	26	3.37	0.47 (0.31-0.72)	0.0004	0.47 (0.31-0.72)	0.0004	0.46 (0.30-0.70)	0.0003
Non-Hodgkin lymphomas	1.35	168	1.88	1.55	18	2.33	0.86 (0.52-1.41)	0.54	0.85 (0.51-1.40)	0.52	0.86 (0.52-1.43)	0.57
Diabetes mellitus	31.47	1,290	21.04	35.78	116	23.11	0.94 (0.78-1.14)	0.53	0.93 (0.77-1.13)	0.49	0.98 (0.81-1.19)	0.86

Abbreviations: IR, incidence rate; PY, person-years; CI, confidence intervals

* Adjusted for age, sex, race/ethnicity

** Adjusted for above plus pre-existing alcohol abuse, drug abuse, HIV, hypertension, cirrhosis, cirrhosis complications, HBV, pre- and post-utilization, treatment experienced, and HCV genotype