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Title:

Direct-acting antivirals for hepatitis C virus induce a rapid clinical and biochemical remission of porphyria cutanea tarda.

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Dear Editor,

Sporadic porphyria cutanea tarda (PCT) is strongly associated with HCV infection in our population [1,2,3,4.] . Therapeutic options for PCT include phlebotomies and low-dose 4-aminoquinolines, which show high rates of disease remission. However, some PCT patients may present frequent relapses attributable to resistance/intolerability/poor adherence to conventional treatments and/or persistence of risk factors. In 2014 we reported the first case of a patient with active PCT and HCV-HIV co-infection cured with direct antiviral agents (DAAs) [5]. Herein, we present a larger cohort of patients, demonstrating the rapid and persistent remission of PCT with DAAs regimes administered for HVC infection.

We treated 16 HVC-infected patients with active PCT from 2014 to 2016 with DAAs. PCT had been previously diagnosed in the Porphyria reference centre of Barcelona according to EPNET protocols and quality control schemes. In all patients, PCT remained clinically and biochemically active despite having been treated with phlebotomies and/or 4-minoquinolines for years. All classic PCT treatments were stopped before the administration of DAAs regimes. Patients included are described in **Table 1**. Examination of risk factors showed that 12 out of the 16 PCT- HCV patients treated with DAAs were co-infected with HIV. None of them had any other PCT- risk factor.

Treatment was administered in all patients according to the EASL Recommendations[6]. We monitored the effect of the DAAs regimes on (a) HCV viral load (b) urine porphyrin levels. All treatments consisted of combinations of antiviral drugs that are known to have comparably high efficacy and safety. Fifteen of the 16 PCT-HCV patients were treated successfully for HCV with DAA regimens. Exceptionally, one patient did not respond due to low treatment adherence.

The registration of HCV viral load, porphyrins in plasma and urine before and after DAAs administration, showed that the eradication of HCV was followed by a decrease in urinary porphyrin concentrations. **Figure 1.**

The normalization of urinary porphyrin levels was followed by PCT clinical remission in all cases. This remission has been maintained over time, and no relapses of PCT have been detected during follow-up (mean: 1,18 years; range: 0-3 years)**.**

Our results show a striking, rapid and complete normalization of porphyrin urinary levels shortly after reaching undetectable RNA-HCV levels in blood tests. This suggests the very clear role of HCV in the maintenance of UROD inhibition rather than a mechanism in which the virus would only indirectly set off a chain of events ultimately leading to PCT. The rapid decline of plasma and urinary porphyrin levels indicates that once the HCV RNA replication is stopped in the hepatocyte, UROD restores its activity.

However, while the eradication of the virus allows a rapid recovery of hepatic UROD activity, there is a long delay between HCV infection and the onset of PCT. The mechanisms involved in this delay and the susceptibility/genetic factors that may predispose a minority of HCV infected patients to develop PCT are still unknown. Further observations showed that PCT patients infected with HCV that reached clinical remission after phlebotomy and/or chloroquine (but presumably with the virus still active) presented a notable proportion of long-standing abnormal (PCT-type) urinary profiles[7], suggesting a direct association between HCV replication within the hepatocytes and the formation of the putative UROD inhibitor.

Until date, only other four cases of PCT-HCV patients successfully treated with DAAs regimes have been reported, however, their HIV/AIDS status was not specified[8, 9.]

Therefore, our results might also help to elucidate the role that HIV infection plays in the development of PCT as most of our patients were co-infected with HIV. Among the co-infected patients (HCV-HIV), the decline of the urinary porphyrin concentration occurred without any change in HIV status. This confirms our previous observations[10], in which we reported that among 8000 patients infected with HIV that attended the Hospital Clinic de Barcelona, there was no case of PCT associated with HIV alone.

The whole set of previous and new results indicate that; (a): the extraordinary effectiveness of new DAAs regimens in the elimination of HCV opens a plausible new approach to the treatment of PCT in which the disease, if associated with HCV infection, could be treated without employing the classic therapeutic options. This clearly opens the path to expand this therapeutic approach as a single and unique therapeutic option in PCT patients with HCV-infection that may cure two diseases with one approach. (b): HIV might not play a direct role in PCT patients; (c): co-infection may reduce the therapeutic efficacy of classic PCT treatments, hence complicating remission; d) DAAs regimes efficacy to cure PCT is not attenuated by HCV/HIV co-infection in patients with undetectable HIV viral load.

Follow-up is still short to completely discard PCT relapse, although the results obtained are encouraging and suggest maintenance of remission over time. For this reason, all patients have been recruited for a specific long-term follow-up program to assess their long-term response.

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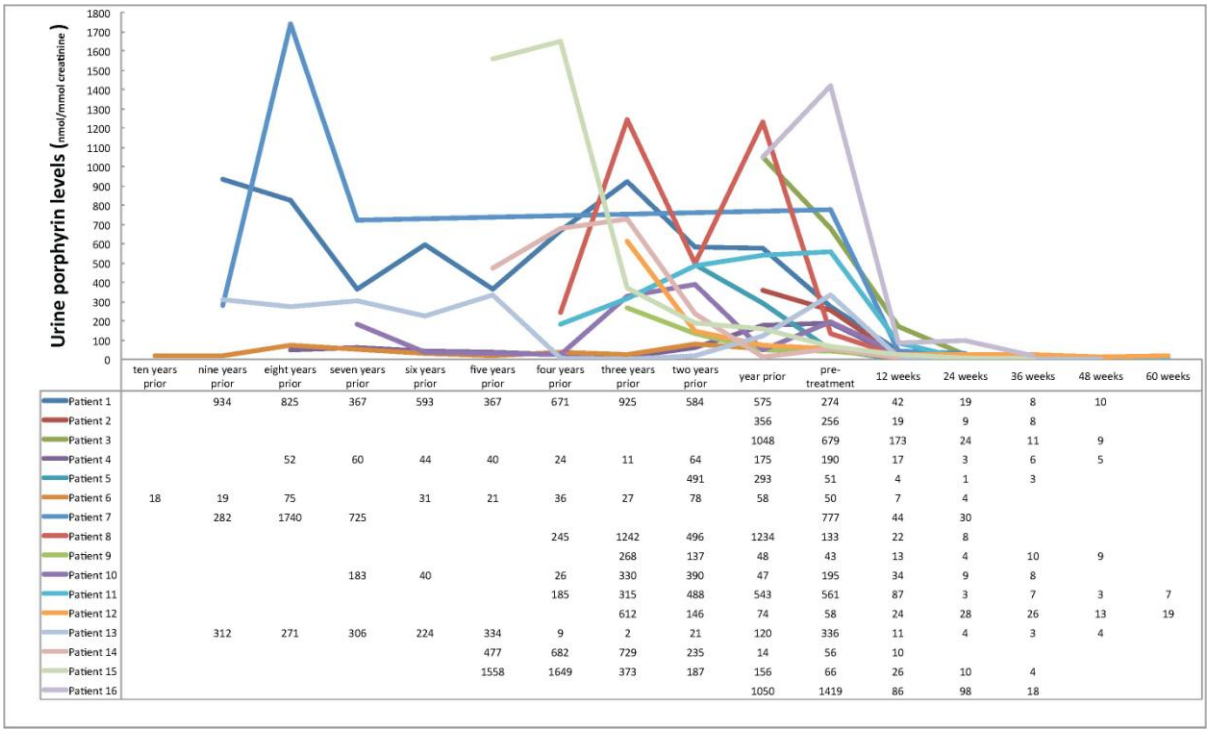
Table 1. Patients included, HIV status, programs of DAAs regimens administered to each patient, HCV viral load and porphyrin urinary levels. (Boc: Boceprevir, Dac: Daclastavir, Das: Dasabuvir, Ebv: Elbasvir, Gzp: Grazoprevir, IFN: Interferon, Ldp: Ledipasvir, Om:Ombitasvir, PegIFN: Pegylated Interferon, Pr: Paritaprevir, Rbv: Ribavirin, Rt: Ritonavir, Sim: Simeprevir, Sof: Sofosbuvir, Tlp: Telaprevir).

Figure 1. Evolution of porphyrin urinary levels over time. A rapid and complete normalization of porphyrin urinary levels was observed immediately post-treatment, and at 12, 24, 48, 60 weeks respectively.

Patient	Age	Sex	Year of PCT diagnosis	HCV infection	HCV genotype	Transient elastography (kPa)	Estimation of METAVIR	HIV infection	CD4 (cel/µl)	HIV viral load (copies/ml)	Previous treatment for HVC	Response to Ifn +Rbv	DAAs regime	Year of DAAs administration	HCV viral load pre-treatment	HCV viral load post-treatment
1	52	M	2004	yes	4			yes	984	<37	no		Dac+Sim+Rbv	2015	2903000	Undetectable
2	62	M	2012	yes	1b	4.7	F0-F1	yes	659	<37	Ifn+Rbv	no	Boc+Rbv+PegIFN	2014	360000	Undetectable
3	56	M	2014	yes	1b	4.5	F0-F1	yes	360	<37	no		Om+Pr+Rt+Rbv	2016	1132875	Undetectable
4	56	M	2006	yes	1b	9.9	F3	no			Ifn+Rbv	no	Ebv+Gzp+Rbv	2014	3864000	Undetectable
5	63	M	2014	yes	1b	5.5	F0-F1	no			no		Om+Pr+Rt+Das	2016	12880	Undetectable
6	54	M	2003	yes	1a			no			Ifn+Rbv	no	Sof+Sim+Rbv	2015	5610000	Undetectable
7	55	M	2007	yes	1b	11.4	F3	yes	596	<37	Ifn+Rbv	no	Sof+Ldp+Rbv	2105	1790000	Undetectable
8	52	F	2012	yes	4	4.8	F0-F1	yes	814	<37	no		Pr+Rt+Om+Rbv	2016	927500	Undetectable
9	53	F	2013	yes	1a	5	F0-F1	yes	492	<37	no		Tlp+Rvb+PegIFN	2015	2206000	13320
10	51	F	2007	yes	4	6.2	F0-F1	yes	1832	<37	Ifn+Rbv	no	Pr+Rt+Om+Rbv	2015	11140000	Undetectable
11	51	M	2011	yes	1a	6.1	F0-F1	yes	651	<37	Ifn+Rbv	no	Boc+PegIFN+Rbv	2014	1904000	Undetectable
12	66	F	2013	yes	4	8.9	F0-F1	yes	434	<37	no		Sof+PegIFN+Rbv	2015	714000	Undetectable
13	60	M	2005	yes	1b	6.8	F0-F1	no			no		Om+Pr+Rt+Das	2015	148000	Undetectable
14	52	M	2011	yes	1a	6.4	F0-F1	yes	824	<37	Ifn+Rbv	no	Sof+Ldp	2015	7209000	Undetectable
15	51	M	2009	yes	3	7.9	F1-F2	yes	847	<37	Ifn+Rbv	no	Sof+Dac	2015	26720	Undetectable
16	53	M	2015	yes	4	9.8	F3	yes	783	<37	Ifn+Rbv	no	Om+Pr+Rbv	2015	342400	Undetectable



	ten years prior	nine years prior	eight years prior	seven years prior	six years prior	five years prior	four years prior	three years prior	two years prior	year prior	pre-treatment	12 weeks	24 weeks	36 weeks	48 weeks	60 weeks
Patient 1		934	825	367	593	367	671	925	584	575	274	42	19	8	10	
Patient 2										356	256	19	9	8		
Patient 3										1048	679	173	24	11	9	
Patient 4			52	60	44	40	24	11	64	175	190	17	3	6	5	
Patient 5									491	293	51	4	1	3		
Patient 6	18	19	75		31	21	36	27	78	58	50	7	4			
Patient 7		282	1740	725							777	44	30			
Patient 8							245	1242	496	1234	133	22	8			
Patient 9								268	137	48	43	13	4	10	9	
Patient 10				183	40		26	330	390	47	195	34	9	8		
Patient 11							185	315	488	543	561	87	3	7	3	7
Patient 12								612	146	74	58	24	28	26	13	19
Patient 13		312	271	306	224	334	9	2	21	120	336	11	4	3	4	
Patient 14						477	682	729	235	14	56	10				
Patient 15						1558	1649	373	187	156	66	26	10	4		
Patient 16										1050	1419	86	98	18		