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Place of therapeutic patient education in chronic hepatitis C treated with direct-acting antivirals

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ABSTRACT

Objective: Today, with the availability of direct-acting antivirals (DAAs), the value of therapeutic patient education (TPE) in chronic hepatitis C needs to be redefined, as these drugs have made treatment simple. The study presented here in sought to define what role TPE plays today in hepatitis C management along with what factors are associated with such programs being used. **Methods:** We included 786 patients mono-infected with hepatitis C virus (HCV) who underwent treatment with DAAs. 284 of whom benefited from a TPE program (36.1%). The characteristics of HCV and how it was treated were compared retrospectively between TPE+ and TPE- patients. The TPE program was overseen by a nurse. **Results:** The following factors were associated with TPE on multivariate analysis: migrant status (OR=3.63, 95%CI: 2.24-5.96, p <0.001), advanced fibrosis (OR=1.73, 95%CI: 1.08-2.76, p=0.022), tobacco use (OR=1.84, 95%CI: 1.10-3.08, p=0.020) and pangenotypic DAA treatment (OR=0.42, 95%CI: 0.26-0.68, p <0.001). Sustained virological response at 12 weeks (SVR 12) was 96% in both groups. **Conclusion:** Overall, TPE was primarily followed by migrants during their HCV management as part of overall medico-psycho-social care, and primarily those with severe disease.**Practice implication:** TPE could help reduce the impact of social inequality on health.

Keywords: hepatitis C, therapeutic patient education, direct-acting antivirals, migrants, advanced fibrosis, tobacco consumption

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Highlights

- TPE in chronic hepatitis C treated with direct-acting antivirals need to be redefined.
- The characteristics of chronic hepatitis C and how it is treated are compared between TPE+ and TPE- patients.
- Migrant status, hepatic advanced fibrosis, tobacco use and pangenotypic direct-acting antivirals are associated with TPE.
- Sustained virological response is high and do not differ between the 2 groups.

Introduction

Now that patients can benefit from direct-acting antivirals (DAAs), the value of therapeutic patient education (TPE) in chronic hepatitis C care requires redefining, as treatment has thus become simple and very safe, with cases of treatment failure rare. The World Health Organization (WHO) defines TPE as a tool to help patients acquire or maintain the skills they need to manage living with chronic disease as best as possible (1). In France, TPE is organized within a legal framework governed by the HPST hospital and healthcare bill (*Hôpitaux, patients, santé, territoires)* (2) and requiring authorization from a regional health agency (*Agence Régionale de Santé - ARS*). This tool is an integrated part of the patient care pathway, with the aim of helping them achieve more independence by facilitating treatment observation and improving their quality of life. The patient thus takes an active role in their own health by getting involved in how their disease is managed. Many studies have proven the value of TPE in HCV treated by interferon, including significantly improved rates of cure, optimized treatment compliance, and reduced obstacles to treatment adhesion (3-5). With the emergence of DAAs, a system of multidisciplinary team (MDT) meetings was implemented in France in December 2014 in regional reference centers under the title of expert services in the fight against viral hepatitis (*Services Experts de lutte contre les hépatites virales – SELHV),* as part of their coordinating mission (6). Each case presented before an MDT was attributed a treatment decision according to how indications and DAA delivery and prescription methods evolved (7-9). The study presented herein sought to define what role TPE plays today in hepatitis C management with DAA treatment, along with what factors are associated with using TPE programs.

Patients and methods

All the patients included in this study were followed-up by the hepato-gastro-enterology department of the Strasbourg university hospital center's (CHU) *Nouvel Hôpital Civil*, and the Alsace SELHV (SELVHA), between January 2015 and December 2019 as part of the SELHVA TPE program authorized by the relevant ARS. All were mono-infected with HCV and completed with DAAs, lasting 8 to 24 weeks, in successive rounds, as recommended by the French Association for the Study of the Liver (*Association française pour l'étude du foie*, AFEF), between January 2015 and February 2019 (10). This was a primary treatment for some or a retreatment for those who presented with reinfection or resistance to an interferon-based treatment. No patient with HCV-HIV coinfection was included in this study due to these patients being followed by a different department.

Two groups of patients were retrospectively compared, classed according to whether or not they received TPE (TPE+ and TPE-). After consultation with the hepatology specialist in charge of the patient's care, each patient was requested their consent to participate in the TPE program. The program was overseen by a SELHVA nurse as part of a program ensuring overall care for the patient's general needs, taking into account physiological, psychological, social and cultural features. As well as the hepatologist and nurse, the TPE team included a psychiatrist specialized in addiction, a social worker, a nutritionist, a

professional interpreter (primarily for Georgian, Russian, and Chechen) and an expert patient. In most cases, the referring general practitioner (GP) was not directly involved in the TPE program, yet remained regularly informed and could rely on the TPE team to follow-up the patient. The TPE program consisted of three distinct steps: 1) an educational diagnosis, established with the patient to get to know them better, identify their needs, and define what skills they still needed to develop or put into practice for better treatment management and improved conditions living with chronic hepatitis C; 2) a personalized care plan (PCP) offered by the pedagogical team, including individual tailored sessions if needed (lasting 45min to 1h); 3) an individual assessment at the end of the program, providing the opportunity to find out how much the patient understood and learnt, creating a report that was then transmitted to their GP. Graded evaluation criteria were defined by the Grand Est ARS, as part of their annual activity report on the TPE program. These included the number of patients that had benefitted from, respectively, an educational diagnosis, a personalized care plane (PCP), an end assessment evaluation, and a full course of the program. In addition, they specify the number of workshops/individual or collective sessions conducted by a member of the team or a TPE-trained patient and the number of personnel directly involved with the patients. Organized by SELHVA, the workshops were provided throughout the care program with the following objectives: 1) to accompany the patient in starting and managing their antiviral treatment; 2) to accompany the patient in managing their comorbidities; 3) to adapt the program to the needs of the patient and any advances made in their treatment.

Patient characteristics were collected from computerized summary reports created by SELHVA which included MDT decisions following the AFEF model (11). These consisted of the following variables: a) demographics: age, gender, and country of birth, with patients born in foreign countries having lived in France for less than six months defined as migrants; b) epidemiology: transmission route, with drug users defined as anyone who had sniffed or injected drugs at least once in their life, according to the criteria outlined in the French ANRS-Coquelicot study (12) and viral genotype; c) clinical and paraclinical data: fibrosis stage, evaluated in the majority of cases using FibroScan®, with elasticity value ≥10kP corresponding to advanced fibrosis (stage F3-F4) (10), hepatocellular carcinoma complicated by cirrhosis, organ transplant, symptomatic cryoglobulinemia, body mass index (BMI) in Kg/m2, related comorbidities (obesity, defined as BMI ≥30 kg/m2, Type 2 diabetes, excessive alcohol consumption exceeding a self-reported 10 standard drinks/week (13) and psychiatric disorder, lifestyle (for alcohol consumption: abstinence or occasional or regular self-reported consumption inferior or superior to 10 standard drinks/week; daily tobacco and cannabis use, no specification of number of cigarettes or joints per day); d) therapy type: primary treatment or retreatment following failed interferon-based treatment, pangenotypic or nonpangenotypic DAAs, opioid substitution therapy (OST) for drug users, drug interactions with DAAs. In addition, sustained virological response assessed at 12 weeks (SVR 12), equating to virological cure, was studied.

All summary reports, stocked on the secure server of the Strasbourg university hospitals (*Hôpitaux Universitaires de Strasbourg* - HUS) were collated in one Excel spreadsheet and anonymized for statistical analysis. The ethics committee of the Strasbourg medical faculty accorded approval for the study on the 17th December 2020 (CE-2020-171). The data analysis was saved on the Strasbourg university hospitals register on the 22nd January 2021 (register reference: 21-009).

The statistical analysis was carried out by the clinical research analysis team (*Groupe Méthode en Recherche Clinique*) from the workplace public health service of the Strasbourg CHU. All analyses were performed using R Studio software. Continuous variables were presented as mean, median with the first and third quartiles. Categorical variables were presented

as numbers and proportion. Regarding the analysis of variables, the first step consisted of univariate analysis, which was performed using a logistic regression model. Results were expressed by means of odd ratio (OR) and the 95% confidence intervals. Each variable of the univariate analysis with a p value ≥ 0.2 was introduced into the multivariate analysis. The multivariate analysis consisted of a logistical regression model performed on the previously-chosen variables. To keep only the most important variables to explain the dependent variable, the criteria of information of Akaike (AIC) were used.

Results

A total of 786 patients mono-infected with HCV and receiving DAA treatment were included, 521 in the TPE- group and 294 in the TPE+ group (36.1%).

Following the evaluation criteria defined by the Grand Est ARS, the patients in the TPE+ group benefitted from an educational diagnosis, 285 from a PCP, and 278 from an end-program assessment report. As a result, 94.5% of patients completed a full program. There were 1,566 workshops conducted, all individual sessions in outpatient care. The number of personnel directly involved with the patients was between five and seven, depending on the year, two of whom were expert patients.

Table 1. Comparison of the characteristics of chronic hepatitis C between the patients with and without therapeutic patient education (TPE) in uni-variate analysis. Abbreviations: a) BMI=body mass index; b) d=drink; c) DAAs=direct-acting antivirals; d) OST=opioid substitution treatment; e) SVR 12=sustained viral response after 12 weeks

Characteristics	total (N=786)			TPE - (N=502)			TPE + (N=284)			P
	n	%	CI 95%	n	%	CI 95%	n	%	CI 95%	
Age median [IQR]	780	55	[31-80.52]	496	56	[32-82]		53	[31-75.93]	<0,001
Sexe										0.036
male	454	57.76	54.22-61.24	276	54.98	50.51-59.39	178	62.68	56.77-68.32	
female	332	42.24	38.76-45.78	226	45.02	40.61-49.49	106	37.32	31.68-43.23	
Native country										<0.001
France	593	75.45	72.28-78.42	425	84.66	81.21-87.7	168	59.15	53.19-64.93	
foreign	193	24.55	21.58-27.72	77	15.34	12.30-18.79	116	40.85	35.07-46-81	
Contamination mode										NS
drug	178	22.65	19.76-25.74	94	18.73	15.41-22.42	84	29.58	24.33-35.26	
transfusion/nosocomial	106	13.49	11.18-16.07	74	14.74	11.76-18.15	32	11.27	7.84-15.53	
others	44	5.6	4.1-7.44	31	6.18	4.23-8.65	13	4.58	2.46-7.7	
unknown	458	58.27	54.73-61.74	303	60.36	55.93-64.67	155	54.58	48.59-60.47	
Genotype										NS
1	490	62.34	58.85-65.74	316	62.95	58.56-67.19	174	61.27	55.33-66.97	
3	148	18.83	16.15-21.74	88	17.53	14.3-21.14	60	21.13	16.53-26.34	
others	132	16.79	14.25-19.59	88	17.53	14.3-21.14	44	15.49	11.49-20.24	
Advanced fibrosis										0.007
yes	360	45.8	42.28-49.36	211	42.03	37.67-46.49	149	52.46	46.48-58.4	
no	416	52.93	49.37-56.46	283	56.37	51.91-60.76	133	46.83	40.91-52.82	
Hepatocellular carcinoma										0.013
yes	30	3.82	2.59-5.4	26	5.18	3.41-7.5	4	1.41	0.39-3.57	
no	756	96.18	94.6-97.41	476	94.82	92.5-96.59	280	98.59	96.43-99.61	

Transplantation										0.040
liver	29	3.69	2.48-5.26	24	4.78	3.09-7.03	5	1.76	0.57-4.06	
kidney	7	0.89	0.36-1.83	5	1.0	0.32-2.31	2	0.7	0.09-2.52	
no	748	95.17	93.42-96.56	472	94.02	91.58-95.93	276	97.18	94.53-98.78	
Cryoglobulin										NS
yes	59	7.51	5.76-9.58	33	6.57	4.57-9.11	26	9.15	6.07-13.13	
no	698	88.8	86.39-90.92	252	90.04	87.08-92.52	246	86.62	82.1-90.35	
BMI (kg/m2)										
median [IQR]	686	24.77	18.27-37.63	439	25.49	[18.36-36.68]	247	25.94	17.86-38.77	NS
< 25	352	44.78	41.27-48.34	227	45.22	40.8-49.69	125	44.01	38.15-50	
25-29,9	218	27.74	24.63-31.01	147	29.28	25.33-33.48	71	25.0	20.07-30.46	NS
>_ 30	113	14.38	12.0-17.03	63	12.55	9.78-15.77	50	17.61	13.36-22.54	
Diabetes										NS
yes	110	13.99	11.64-16.62	70	13.94	11.03-17.29	40	14.08	10.26-18.68	
no	676	86.01	83.38-88.36	432	86.06	82.71-88.97	244	85.92	81.32-89.74	
Psychiatric comorbiditis										0.003
yes	124	15.78	13.3-18.52	66	13.15	10.32-16.42	58	20.42	15.89-25.59	
no	564	71.76	68.47-74.88	381	75.9	71.91-79.58	183	64.44	58.57-70	
Alcohol										NS
< 10 d/week	53	6.74	5.09-8.73	42	8.37	6.10-11.14	11	3.87	1.95-6.82	
> 10 d/week	32	4.07	2.8-5.7	15	2.99	1.68-4.88	17	5.99	3.53-9.41	
none or occasional	672	85.5	82.84-87.88	429	85.46	82.07-88.43	243	85.56	80.93-89.44	
Tobacco										<0.001
yes	136	17.3	14.72-20.13	69	13.75	10.85-17.07	67	23.59	18.78-28.97	
no	396	50.38	46.83-53.93	278	55.38	50.91-59.78	118	41.55	35.76-47.52	
Cannabis										0.008
yes	36	4.58	3.23-6.28	16	3.19	1.83-5.12	20	7.04	4.35-10.67	
no	492	62.6	59.11-65.99	329	65.54	61.2-69.69	163	57.39	51.42-63.22	
Primary treatment										NS
yes	524	66.67	63.25-69.96	327	65.14	60.79-69.31	197	69.37	63.65-74.68	
no	262	33.33	30.04-36.75	175	34.86	30.69-39.21	87	30.63	25.32-36.35	
Type of DAAS										p<0.001
pangenotypic	166	21.12	18.32-24.14	126	25.1	21.36-29.13	40	14.08	10.26-18.68	
no pangenotypic	620	78.88	75.86-81.68	376	74.9	70.87-78.64	244	85.92	81.32-89.74	
OST										NS
yes	97	54.49	46.88-61.96	52	55.32	44.71-65.59	45	53.57	42.35-64.53	
no	81	45.51	38.04-53.12	42	44.68	34.41-55.29	39	46.43	35.47-57.65	
Drug interactions										NS
yes	129	16.41	13.89-19.19	90	17.93	14.67-21.57	39	13.73	9.95-18.29	
no	657	83.59	80.81-86.11	412	82.07	78.43-85.33	245	86.27	81.71-90.05	
SVR 12										NS
yes	759	96.56	95.04-97.72	486	96.81	94.88-98.17	273	96.13	93.18-98.05	
no	21	2.67	1.66-4.06	10	1.99	0.96-3.63	11	3.87	1.95-6.82	

All patient characteristics are detailed in *Table 1*. Mean age was 55.4 years with a male majority (58%). Three quarters of the patients were native French. Of all the migrants, 90% originated from eastern Europe, primarily Georgia, Belarus, Chechnya, Kosovo and Bosnia; the

others were of north-African, sub-Saharan African or central Asian origin. The reasons for immigrating were primarily economic, with political or safety concerns rarer. The majority of the migrant patients were in vulnerable situations, yet still had health cover at the time of the MDT, enabling them access to healthcare. For the most part, this was provided by the French universal healthcare program (*Couverture Maladie Universelle Complémentaire - CMUc*) (which became *Complémentaire santé solidaire* in 2019) or state medical aid (*Aide Médicale d'Etat - AME*) plan. Infection was primarily caused through drug use, although the transmission route was unknown in nearly 60% of patients. Genotype 1 was predominant (62.3%). Advanced fibrosis was reported in 45.8% of patients. Hepatocellular carcinoma and history of liver or kidney transplant were rare (<5%). Less than 10% presented with symptomatic cryoglobulinemia, with no lymphoma. Mean BMI was 25.6Kg/m^2. The proportion of obesity, diabetes, or psychiatric comorbidity was near 15%. Excessive alcohol consumption was rare (4%). Daily tobacco use was nearly 20%, while cannabis use did not exceed 5%. Two-thirds of patients were prescribed DAAs for a primary treatment. Nonpangenotypic DAAs were prescribed to over three-quarters of patients. OST was prescribed to over half the drug users. Drug interactions with DAAs were present in 16% of patients. SVR 12 was observed in 96.5% of patients.

Comparisons between TPE- and TPE+ patients on univariate analysis are detailed in *Table 1*. The patients who benefitted from TPE were younger (p <0.001), more often male (p=0.036) and not of French origin (p <0.001). They more frequently presented with advanced fibrosis (p=0.007), hepatocellular carcinoma (p=0.013), history of liver or kidney transplant (p=0.04), or psychiatric comorbidity (p=0.003). Tobacco and cannabis use was more common in this group (p <0.001 and p=0.008) as was nonpangenotypic DAA administration (p <0.001). There was no significant difference between the two groups for the other parameters. Similarly, SVR 12 did not differ: 96.8% in the TPE- group and 96.1% in the ETP+ group.

Table 2. Factors associated with therapeutic patient education (TPE) in multi-variate analysis. Abbreviation: DAAs=direct- acting antivirals

Characteristics	OR	95% CI	p value
Migrant	3.63	2.24-5.96	<0.001
Advanced fibrosis	1.73	1.08-2.76	0.022
Tobacco consumption	1.84	1.10-3.08	0.020
Pangenotypic DAAs	0.42	0.26-0.68	<0.001

In multivariate analysis (Table 2), migrant status (OR=3.63, 95%CI: 2.24-5.96, p<0.001), advanced fibrosis (OR=1.73, 95%CI : 1.08-2.76, p=0.022), and tobacco consumption (OR=1.84, 95%CI : 1.10-3.08, p=0.020) were positively associated with TPE, while treatment with pangenotypic DAAs (OR=0.42, 95%CI : 0.26-0.68, p<0.001) was negatively associated.

Discussion and conclusion

Discussion

Overall, this comparative study revealed TPE to be associated with a vulnerable population, that of migrants, as well as with the severity of liver disease, cannabis use and particularly tobacco use, and type of DAAs administered. Nevertheless, this was a retrospective study and was limited to only a hospital population. Furthermore, the results are affected by what DAA prescription and dispensing conditions were employed within the legal framework of MDTs in France in the years 2014 to 2019. Initially, DAAs were prescribed by hospital-based specialists, dispensed by pharmacies within medical centers. The indications were restrictive, applying to chronic HCV in adults with advanced F3-F4 fibrosis or an associated HIV infection, systemic and symptomatic mixed cryoglobulinemia, or B-cell lymphoma (6). In July 2016, the treatment indication was extended to patients with Stage F2 fibrosis (7). Then, from August 2017, it was

extended to all stages of fibrosis, with MDTs limited to complex cases with advanced F3-F4 fibrosis or comorbidities (8). In March 2018, pharmacies outside hospital structures were also authorized to dispense DAAs and in May 2019, the prescription of pangenotypic DAAs became universal to simplify HCV treatment (16).

In our study, TPE had no effect on therapeutic efficacy, as opposed to what previous studies have reported for interferon (3-5). The SVR 12 rate was identical (96%) and in line with that reported in therapy trials (14). The TPE program was completed by 94.5% of patients, and the great number of workshops was probably due to the large proportion of migrant patients (40.85%).

The association between TPE and the migrant population can be explained by it affording the possibility of a global approach presenting the disease as part of life, and the cure as an ongoing project, keeping in mind that curing the virus does not mean curing the patient, and that therapeutic care is not limited to just antiviral administration. By mobilizing a multidisciplinary team with specific permanent locations, it is easier to talk with the patient about both their pathology and how it relates to aspects of their personal and social life, as well as discussing any potential use of psycho-active agents (15). The involvement of a nurse trained in TPE, as was the case in our study, is especially justified considering that DAA treatment is safe and easy to follow (15). Having high-quality communication and interactions with patients is essential in order to explain the treatment and adequately follow their progress, as well as for prevention, hence the importance of having a professional interpreter, specialized for such work, for those patients who cannot speak French well, as we did in our study (16,17). This also helps develop a better understanding of psychiatric disorders, found to be more common in the TPE+ group on univariate analysis.

The association between TPE and severity of liver disease was also demonstrated in this study. TPE was associated not only with advanced fibrosis on univariate and multivariate analysis, but also with hepatocellular carcinoma and history of liver transplant on univariate analysis. Advanced fibrosis was particularly found to be more common in the TPE+ group than the TPE- (52% *vs.* 42%). The clearer male predominance within the TPE+ group on univariate analysis could provide an explanation for this, given that male gender is an independent factor of fibrosis progression in HCV (14,18). Nevertheless, the patients in the TPE+ group were younger on univariate analysis, and age is also a recognized factor in fibrosis progression (18). On the other hand, the frequency of other factors likely to be involved, such as excessive alcohol consumption, obesity, and diabetes (14,18), did not differ between the two patient groups. The higher incidence of advanced fibrosis in our study is probably linked to our inclusion criteria, which selected patients from MDTs that prioritize severe forms of HCV with advanced fibrosis.

Among the different psycho-active agents being used, only tobacco use was associated with TPE on uni- and multi-variate analyses. We thus believe that addictology care and management in TPE should not be limited to drugs and alcohol, especially given that tobacco is susceptible to exacerbate HCV progression to hepatocellular carcinoma (19,20). The proportion of drug users was higher in the TPE+ group in our study (29.58% *vs.* 18.73%), distribution across different transmission routes, however, did not differ significantly between the TPE+ and TPE- groups. Drug multiuse is also known to be common among drug users (21), although this was not analyzed in our study. Similarly, the actual level of tobacco use, as well as that of cannabis, was not analyzed in our study.

The last variable associated with TPE was DAA type. On uni- and multivariate analysis, pangenotypic DAAs were less often administered to TPE+ patients due to their administration being simpler with fixed courses of 8 or 12 weeks. For those taking nonpangenotypic DAAs, the treatment course could last up to 6 months. Furthermore, at the beginning of our study, these DAAs could be associated with ribavirin in some cases (10,14). TPE also enabled drug interactions to

be better managed, and these were found to be less common in the TPE+ group, although not significantly different from those of the TPE- group.

Conclusion

TPE has evolved with the emergence of DAAs for hepatitis C treatment. These programs offer global, medico-psycho-social care that particularly benefits migrant populations who were often in vulnerable situations. On assessing the results, it is now advisable to widen criteria to include patient quality of life and overall improvement in their health, rather than just focusing on HCV cure.

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Conflicts of interest

The authors state that they have no competing interests with regard to the content of this paper.

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