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Use of Antiviral Therapy in Patients with Chronic Hepatitis C in Pakistan

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Introduction

Aims: We compared antiviral therapy outcomes in treated and untreated patients with hepatitis C and decompensated cirrhosis.

Methods: Decompensated cirrhosis and HCV patients were treated in 2019.Sofosbuvir, ledipasvir or daclatasvir, with or without ribavirin was the choice of treatment by physician. For functional outcome comparison, untreated patients with HCV and decompensated cirrhosis were retrospectively studied who were registered on a database 6 months before treatment. virological response 12 weeks post antiviral treatment (treated cohort) was primary endpoint

Results: 467 patients received treatment (409 decompensated cirrhosis). In 381 patients (81.6%) – 209 from 231 (90.5%) with genotype 1 and 132 from 192 (68.8%) with genotype 3 viral clearance were achieved. MELD scores improved in treated patients (mean change 0.85) but worsened in untreated patients (mean + 0.75) (p 65 or with low (<135 mmol/L) baseline serum sodium concentrations were least likely to benefit from therapy.

Conclusions: All oral DAAs effectively cured HCV in patients with advanced liver disease. Overall virological response was high and we found early improvement in liver parameters and in clinical outcomes after antiviral treatment, compared to untreated patients.

Keywords: Hepatitis C Virus, Sofosbuvir, Ledipasvir, Daclatasvir, MELD Score, Decompensated Cirrhosis

Introduction

The presence of background hepatitis C virus (HCV) infection cannot be overestimated in view of the prevalence of chronic hepatitis C (CHC) and the risk of adverse outcomes of this disease. Experts predict that in 10-20 years HCV infection will be an immense medical, social and economic problem [1-5]. At present, 0.5-2% of the population has been diagnosed with CHC. The frequency of newly diagnosed cases of HCV infection in developed countries ranges from 1 to 5 cases per 100 000 population (true frequency exceeds these indicators by 5-8 times). For the Commonwealth of Independent States (CIS), the incidence of newly diagnosed cases of HCV infection is 60-80 per 100 000 people [6]. Even worse statistics exist for Ukraine. In recent years, the prevalence of HCV in Ukraine amounted to 612 people per 100 000 [5, 6.]

End-stage HCV is a major indication for liver transplantation. Unfortunately, for most patients with CHC in Ukraine, this operation is not available. Pathogenic treatment of CHC is based on antiviral therapy, aimed at the elimination of the virus, slowing the progression of the disease, and reducing the risk of hepatocellular carcinoma.

Serious deficiencies in today's regimens include the high cost of modern drugs used for treatment of HCV, longer duration of treatment and the high frequency of adverse reactions during treatment with antiviral drugs (flu-like symptoms with fever, myalgia, depression, psychosis, decrease in white blood cells, thrombocytopenia, anemia, and autoimmune reactions). Thus, these data suggest the need to develop effective and affordable methods of pathogenic therapy for the volume of cases of HCV. Currently, treatment options for HCV patients worldwide are associated only with the use of drugs, without considering whether to use resort (spa) resources with these patients [7-10]. Therefore, the purpose of this study was to evaluate the effectiveness of combined use of antiviral therapy in patients with CHC in the replication phase.

Methodology

Patients enrolled who received antiviral therapy between 1 April 2019 and 11 august 2019 were studied. Eligible patients were those at significant risk of death or irreversible damage from HCV infection within 12 months, irrespective of genotype. Criteria for inclusion were decompensated cirrhosis – ascites, variceal bleed or encephalopathy (past or current), Child Pugh score P7, or non–hepatic manifestation of HCV likely to lead to irreversible damage in 12 months and intolerant to, or failed, PegIFN and ribavirin therapy, or exceptional circumstances (determined by a review panel).

Treatment was chosen by the prescribing clinician and involved either ledipasvir/sofosbuvir or sofosbuvir/daclatasvir, both with or without ribavirin for a total of 12 weeks.

For the comparator population (untreated) we used a retrospective, observational study design. Patients were selected from the HCV Research database. Inclusion criteria were decompensated cirrhosis (defined by the criteria above) who were enrolled before 1 October 2018 and patients subsequently included in the EAP who had been enrolled in the database 6 months prior to the initiation of therapy.

Treatment All patients received a maximum of 12 weeks therapy. Sofosbuvir (400 mg per day) chose to combine it with either ledipasvir (90 mg per day), as a single tablet co-formulation with sofosbuvir, or with daclatasvir (60 mg per day, with dose adjustment to 30 mg or 90 mg per day as recommended in patients with relevant potential drug-drug interactions). Inclusion and dosage of ribavirin was discretionary according to the treating clinician. Monitoring Patients receiving therapy were reviewed at treatment weeks 2, 4, 8 and 12, and post treatment weeks 4 and 12. Clinical events were recorded on a standardized form and local accredited laboratories measured serum creatinine, bilirubin, albumin, alanine aminotransferase (ALT), sodium, HCV RNA level, full blood count and clotting profile, which were recorded for each study visit. Missing or late values during therapy were ignored, and missing values from the initiation visit or week 12 post treatment visit were derived from the nearest adjacent test value taken before or after therapy respectively. MELD scores were calculated centrally using site-derived laboratory parameters. Serious adverse events, specifically any hospital admissions, decompensation events, liver transplantation, other complications of end-stage liver disease (including hepatocellular carcinoma) and death were recorded. Baseline demographic data (age, gender, ethnicity, body mass index (BMI), alcohol use, previous treatment history, decompensation events and HIV serostatus).

Outcome measures the primary outcome was sustained virological response 12 weeks post treatment (SVR12) defined as undetectable HCV RNA measured at an accredited local laboratory with a lower limit of quantification (LLQ) of < 30 IU/ml. Secondary outcomes

included change in MELD score, and adverse clinical events during the study period. Overall adverse clinical outcome was defined as the composite of a MELD score increase by 2 points or more, and/or occurrence of any serious adverse event. For patients who were enrolled in the comparator cohort, the responsible clinician reported the same events in a pre-defined form. All analyses were by intent to treat – patients.. Data analysis Chi-square were used for primary analysis. Logistic regression analysis were used for Predictors of relapse were also assessed in which only patients with a known virological outcome were included.

Results

Treatment cohort A total of 480 patients received therapy as part of the EAP between the start of the programme (1 April 2019) to 11 august 2019; 467 patients consented to provide data. At the start of treatment 409 (88%) patients had decompensated cirrhosis and/or Child Pugh score P7 liver transplantation with aggressive HCV recurrence without decompensation undergone with 44 patients.. 14 (3%) patients were treated for extrahepatic indications. Table 1 show the baseline characteristics of the treated cohort. A higher ratio of genotype 3 patients received daclatasvir compared to genotype 1 (125/192 (65%) vs. 46/231(20%)), and physicians prefer to add ribavirin to their treatment regimen for most (427/467 (91%)) patients (Table 2)

For patients with decompensated cirrhosis, we assessed whether baseline characteristics might be useful in predicting functional benefit gained from therapy. Patients older than 65 years with reduced synthetic function (serum albumin 635 g/L) had the lowest odds of deriving functional benefit with antiviral treatment (Table 3).

Table 1. Baseline characteristics of treated and comparator (untreated) patients.

Characteristic		Treated cohort				Untreated cohort
			All (%)	Decompensated hepatic	Baseline liver Total (%) transplant	Extra indication
Total patients		467	409	44	14	261
Age (years)	Median	54 (28-80)	54 (28-79)	62 (32-75)	58 (35-80)	54 (33-77)
Gender	Male	339 (72.6%)	297	35	7	214 (82.0%)
Ethnicity	Caucasian	347 (74.3%)	302	34	11	230 (88.1%)
Prior therapy	Yes	284 (60.8%)	244	33	7	162 (62.1%)
	With DAA*	17 (3.6%)	14	3	0	
HIV infected	Yes	23 (4.9%)	20	2	1	6 (2.3%)
Virology						
Genotype	1	231 (49.3%)	200	26	5	129 (49.4%)
	3 192 (41.1%)	172	14	6	90 (34.5%)	
	Other	44 (9.4%)	37	4	3	42 (16.1%)
Viral load (IU/ml)	Median	280,511	255,279.5	1,006,189	2,091,786	208,688
	Range	(17-17,835,823)	(17-13,613,875)	(71.5-17,835,823)	(2189-7,838,385)	(80-23,100,000)
Liver/renal status						
Bilirubin (µmol/L)	Median, range	27(4-433)	28 (4-433)	18 (5-82)	14 (5-30)	26 (3-335)
Albumin (g/L)		31 (17-55)	31 (17-55)	35 (23-48)	36 (29-46)	32 (10-46)
MELD		11 (6-32)	12 (7-32)	11 (6-25)	10 (6-15)	11 (6-32)
Creatinine (µmol/L)		69 (32-477)	66 (32-477)	98 (60-286)	75 (48-206)	68 (25-340)
ALT (U/L)		53 (8-594)	54 (8-345)	44 (17-594)	48 (24-156)	
Platelets ($x10^9$/L)		74 (3-321)	72 (20-277)	116 (3-321)	114 (17-233)	70 (3-358)
Child Pugh score	B n (%)	319 (68.3)	297 (72.6)	21 (47.7)	0 (0.0)	
	C 43 (9.2)	41 (10.0)	2 (4.5)	0 (0.0)		

Ascites	Present	197 (42.2)	183 (44.7)	14 (31.8)	0 (0.0)	
Alcohol use	Current	59 (12.6%)	53	3	3	60 (23.0%)
	Never	95 (20.3%)	80	10	5	53 (20.3%)
	Past	281 (60.2%)	246	31	4	135 (51.7%)
	Unknown	32 (6.9%)	30	0	2	13 (5.0%)
Treatment	SOF/DCV	15 (3.2%)	12	1	2	
SOF/DCV/RBV		172 (36.8%)	150	17	5	
SOF/LDV		25 (5.4%)	18	7	0	
SOF/LDV/RBV		255 (54.6%)	229	19	7	

Table 2. Choice of treatment regimens according to HCV genotypes and virological response at 12 weeks post-treatment (SVR12) in patients treated on the expanded access programme.

	Treatment regimen	All patients (n = 467)			Decompensated patients (n = 409)			OLT before baseline (n = 44)			Extrahepatic patients (n = 14)		
		SVR12	n	%	SVR12	n	%	SVR12	n	%	SVR12	n	%
All patients	All	381	467	81.6	329	409	80.4	38	44	86.4	14	14	
	SOF/DCV	11	15	73.3	8	12	66.7	1	1	100.0	2	2	
	SOF/DCV/RBV	133	172	77.3	114	150	76.0	14	17	82.4	5	5	
	SOF/LDV	18	25	72.0	13	18	72.2	5	7	71.4	0	0	
	SOF/LDV/RBV	219	255	85.9	194	229	84.7	18	19	94.7	7	7	
Genotype 1	All	209	231	90.5	179	200	89.5	25	26	96.2	5	5	
	SOF/DCV	3	5	60.0	2	4	50.0	1	1	100.0	0	0	
	SOF/DCV/RBV	36	41	87.8	30	34	88.2	5	6	83.3	1	1	
	SOF/LDV	16	18	88.9	11	13	84.6	5	5	100.0	0	0	
	SOF/LDV/RBV	154	167	92.2	136	149	91.3	14	14	100.0	4	4	
Genotype 3	All	132	192	68.8	117	172	68.0	9	14	64.7	6	6	
	SOF/DCV	5	7	71.4	3	5	60.0	0	0	-	2	2	
	SOF/DCV/RBV	86	118	72.9	75	105	71.4	8	10	80.0	3	3	
	SOF/LDV	2	7	28.6	2	5	40.0	0	2	0.0	0	0	
	SOF/LDV/RBV	39	60	65.0	37	57	64.9	1	2	50.0	1	1	
Other	All	40	44	90.9	33	37	89.2	4	4	100.0	3	3	
	SOF/DCV	3	3	100.0	3	3	100.0	0	0	-	0	0	
	SOF/DCV/RBV	11	13	84.6	9	11	81.8	1	1	100.0	1	1	
	SOF/LDV	-	0	-	0	0	-	0	0	-	0	0	
	SOF/LDV/RBV	26	28	92.8	21	23	91.3	3	3	100.0	2	2	

SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; OLT, orthoptic liver transplant.

Table 3. Likelihood of functional benefit (no MELD increase and no serious adverse events) or adverse outcome (MELD increase and/or serious adverse events) following antiviral therapy based on patient baseline characteristics.

			Adverse outcome (n)	Benefit (n)	Benefit %	Odds ratio	95 % CI
Age/albumin (g/L) interaction terms	Age <65	Albumin ≥35	34	52	60.5	1 (Ref)	
	Age <65	Albumin <35	159	124	43.8	0.52	0.32-0.86
	Age ≥65	Albumin ≥35	6	6	50.0	0.67	0.20-2.27
	Age ≥65	Albumin <35	17	11	39.3	0.44	0.18-1.05
Baseline serum sodium	≥135		135	141	51.1	1 (Ref)	
(mmol/L)	<135		81	52	39.1	0.63	0.41-0.97

Discussion

The efficacy of all oral antiviral regimens in the management of patients with compensated liver disease due to chronic HCV infection is now established [11–14] and data on patients with decompensated cirrhosis are emerging [5–7, 14]. In this study we examined a fixed, 12 week, duration course of antiviral therapy in a large heterogeneous group of patients with decompensated cirrhosis or life-threatening complicated infection of HCV, and outcomes of an untreated cohort with treated disease and duration of follow-up were compared with each other in this study.

The EAP study was robustly conducted with prospective, standardised monitoring and reporting through a central database. The inclusion criteria for treatment for current study were similar to other studies of HCV treatment in decompensated patients (SOLAR-1, ASTRAL-4) [6, 14].17% patients were Child Pugh class A at baseline within the decompensated subgroup. Importantly for the comparator group we recruited patients who enrolled in the cohort prior to therapy was available to reduce the chance of inherent bias in selecting treated patients with prior follow-up.

Conclusion

All oral antiviral therapy drugs effectively cured HCV in patients with advanced liver disease. Overall virological response was high, in current study we found that, compared to untreated patients, patients who took antiviral treatment had better clinical outcomes and also improvement in the parameters of liver.

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