NATURAL COURSE OF TREATED AND UNTREATED CHRONIC HCV INFECTION IN GREECE: RESULTS OF THE NATIONWIDE *HEPNET* STUDY

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BACKGROUND/AIMS

The natural course of chronic hepatitis C (CHC) is variable and there is considerable debate whether interferon (IFN)-based treatments radically affect it. Moreover the management of therapy and its effect on the clinical progression of chronic HCV infection in Greece has not been studied nationwide. This study aimed to evaluate the effect of treatment on the Greek HCV infected population taking advantage of a large sample with a wide geographical coverage of Greek Hepatology Clinics.

METHODS

We retrospectively analyzed 1434 cases of CHC from 30 Centers throughout Greece (median age 38, interquartile range [IQR] 28.5-53.7 years; 59.4% males) followed during 1997-2004 for median time of 3.8 (IQR 1.5-7.3) years. Patients with HIV or HBV co-infection and children (age≤14 years at study entry) were excluded. The first diagnosis of a clinical condition such as liver decompensation, HCC, transplantation or death was the endpoint under consideration. Time to clinical progression and the effect of prognostic factors were analyzed using Cox proportional hazards models, while treatment, sustained response and cirrhosis were considered as time-dependent covariates.

RESULTS

During the follow-up a total of 68 (4.7%) subjects developed a clinical event. In 48 (70.6%) cases of them the diagnosis was liver decompensation, in 14 (20.6%) hepatocellular carcinoma, while 6 (8.8%) subjects died before developing any other event. The duration of HCV infection could be estimated in 796 cases (54.8% IDU-, 45.2% transfusion-related), whereas in 885 cases the genotype was known (Table 1). Of the 1434 patients, 792 (55.2%) had completed an IFN-based treatment course including at least 6 months post-treatment observation, 25 treated patients were excluded because of missing data and 617 (43.0%) cases had remained untreated. For about 79% of treated subjects both sustained biochemical (SBR) & virological (SVR) response were observed.

Table 1. Characteristics of the study population by presence of clinical event*

	Clinical Event			
	Yes n (%)	No n (%)	Total n (%)	p-value
Gender				0.034
Male	32 (3.8)	820 (96.2)	852 (59.4)	
Female	36 (6.2)	546 (93.8)	582 (40.6)	
Age (years)				<0.001
≤ 29	4 (1.1)	376 (99.0)	380 (26.5)	
29 - 38	6 (1.8)	328 (98.2)	334 (23.3)	
38 - 54	14 (3.8)	354 (96.2)	368 (25.7)	
> 54	44 (12.5)	307 (87.5)	351 (24.5)	
BMI (kg/m^2)				0.294
≤ 25	21 (4.1)	495 (95.9)	516 (50.9)	
25-30	12 (3.2)	361 (96.8)	373 (36.9)	
>30	8 (6.4)	117 (93.6)	125 (12.3)	
Genotype				0.246
Type 1	15 (3.7)	390 (96.3)	405 (45.8)	
Type 2,3,5	6 (1.7)	339 (98.3)	345 (39.0)	
Type 4	3 (2.2)	132 (97.8)	135 (15.3)	
Source of Infection				<0.001
IDU	6 (1.3)	466 (98.7)	472 (32.9)	
Transfusion	14 (3.9)	346 (96.1)	360 (25.1)	
Other	6 (4.1)	142 (96.0)	148 (10.3)	
Unknown	42 (9.3)	412 (90.8)	454 (31.7)	
Therapy				0.001
No	41 (6.7)	576 (93.4)	617 (43.8)	
Yes	23 (2.9)	769 (97.1)	792 (56.2)	
SBR				<0.001
No	21(4.8)	414 (95.2)	435 (54.9)	
Yes	2 (0.6)	355 (99.4)	357 (45.1)	
SVR				0.005
No	21(4.2)	483 (95.8)	504 (63.6)	
Yes	2 (0.7)	286 (99.3)	288 (36.4)	
Cirrhosis				0.131
No	22 (3.4)	629 (96.6)	651 (85.6)	
Yes	7 (6.4)	103 (93.6)	110 (14.5)	

** Progression to liver decompensation, HCC, transplantation or death, whichever was first*

Results from univariate Cox proportional hazards models are presented in Table 2. Older age at diagnosis was significantly related to disease progression. The duration of HCV infection had only a marginal effect on events (P=0.083), while source of infection, genotype and body mass index had non-significant effect.

Table 2. Factors associated with clinical progression. Results from univariate Cox proportional hazards models.

	HR	95%CI	p-value
Gender			
Female / Male	1.68	1.04-2.72	0.034
Age			
per 10 yrs increase	2.15	1.78-2.60	<0.001
Age category			
29-38 ετών /≤29 ετών	2.08	0.59-7.42	0.257
38-54 ετών /≤29 ετών	4.50	1.46-13.86	0.009
>54 ετών /≤29 ετών	17.10	6.05-48.58	<0.001
Infection time			
per 10 yrs increase	1.43	0.96-2.14	0.083
SBR*			
no SVR / no therapy	1.22	0.72-2.05	0.461
SVR / no therapy	0.26	0.06-1.08	0.064
Cirrhosis*			
Yes / No	3.68	1.63-8.33	0.002

** time-dependent covariate*

Results from multivariate Cox proportional hazards models are presented in Table 3. Women were significantly older than men in the study population, therefore the significant effect of gender disappeared after adjusting for age. Results from time-dependent multivariate Cox proportional-hazards models showed that patients with a SBR had significantly lower hazard for developing a clinical event compared to non-treated patients. The beneficial effect was not maintained in non-SBR patients, whereas the detrimental effect of older age at diagnosis remained highly significant. Similar results regarding the size of the effect revealed for those having SVR, although due to the smaller number of cases with known virologic response status the nominal significance level (ie. 5%) was not reached.

Table 3. Factors associated with clinical progression. Results from multivariate Cox proportional hazards models.

	HR	95% CI	p-value
SBR			
no SVR / no therapy	0.80	0.46-1.39	0.432
SVR / no therapy	0.22	0.05-0.92	0.038
Age			
per 10 yrs increase	2.12	1.73-2.58	<0.001

Further analysis revealed a significant interaction (p=0.001) between treatment and age, indicating that treatment was particularly beneficial in patients more than 54 years old at HCV diagnosis.

Table 4. Results from Cox proportional hazards models including age and treatment interaction.

	HR	95% CI	p-value
Age ≤ 54 years			
therapy / no therapy	2.10	0.91-4.86	0.082
Age > 54 years			
therapy / no therapy	0.34	0.17-0.67	0.002

CONCLUSIONS

- **IFN-based treatments alter the natural course of chronic HCV infection.**
- **A protective effect is present in patients with sustained response.**
- **Older patients, at higher risk of events, gain the greatest benefit from treatment.**