JMSR
Journal of Medical and Surgical Research

Research Article

ISSN: 2351-8200

JMSR 2016, Vol III; N°1: 223 - 228

Hepatocellular Carcinoma screening is indicated Even After Sustained Virological Response: Moroccan University Hospital Experience-

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Abstract

Introduction: Hepatitis C is the first aetiologic agent for HCC in Morocco. Antiviral treatment reduces the risk of developing HCC in patients with chronic hepatitis C but few cases of HCC have been still reported. We aimed to define population with high risk of HCC occurrence, confirm the protective role of SVR and to identify predictive factors of developing HCC after SVR. We'll try to present suggestions about screening strategies (indications and interval) after antiviral therapy according to level of HCC occurrence risk.
Patients and Methods: We included all patients with chronic hepatitis C treated in our department from January 2002 to April 2010. We compare HCV-treated patients with no developed HCC to HCC population using khi-2 and Fisher Exact analysis.
Results: 369 patients treated for hepatitis C were considered, and 20 HCC were reported. The risk of HCC occurrence was not significant according to gender and genotypes. Advanced age and severe fibrosis were significant risk factors. HCC was reported in 2.3% of sustained virological responders versus 12.5% of non responders. SVR is a significant protective factor.
Conclusion: In our series, 5% of previously treated HCV carriers developed HCC and 2.3% of sustained virological responders developed HCC. Achieving SVR after antiviral therapy is a protective factor. Advanced age (> 50 y. o), severe fibrosis (F>2) and lack of SVR at HCV diagnosis are predictive factors of HCC development in treated patients. Regular bi-annual ultrasonography screening should be indicated necessarily in patients with advanced fibrosis stage (F3- F4) even after SVR, particularly when co-morbid conditions are associated (advanced age, NASH, diabetes mellitus,…). Screening interval in sustained virological responders with reduced fibrosis stage may be reduced to annual surveillance. Establishing guidelines about consensual strategy to survey sustained virological responders is now necessary especially with high rates of SVR and the extension of treatment indications in era of DAA drugs.

Keywords: Hepatocellular carcinoma; Screening strategy; Sustained virological response (SVR):

Introduction

Hepatitis C virus (HCV) is a recognized aetiologic agent that induces carcinogenesis process in the liver by generating inflammation, fibrosis, and a carcinogenic tissue microenvironment for the development of Hepatocellular Carcinoma (HCC).
HCC is the most common malignant tumors in the world; it's also the main type of primary liver cancers and the third most common cause of cancer mortality worldwide [1]. In Morocco, according to our department register, the major risk factor for

JMSR
Journal of Medical and Surgical Research
Research Article
ISSN: 2351-8200
JMSR 2016, Vol III; N°1: 223- 228

HCC is chronic hepatitis especially hepatitis C virus infection [2]. The risk of HCC gradually increases as liver fibrosis progresses and HCV-induced HCC is a rational target for cancer preventive intervention. Once cirrhosis is established, the annual incidence of HCC is extremely high (1%-7% per year) [3]. Hepatocarcinogenesis is an heterogeneous and long process and there is still much to elucidate. The combination of pegylated interferon to ribavirin (PEG/RBV) given for 24 or 48 weeks -according to genotype- has been retained for long years ago as the only consensual and standard treatment of chronic hepatitis C before the development of antiproteasis and anti polymerases. Recent clinical trials have reported sustained virological response (SVR) rates greater than 90% with the use of Direct-Acting Antiviral drugs (DAA)-based interferon-free regimens even in cirrhotic and hard-to-treat patients [3]. Antiviral treatment limits fibrosis progression and the incidence of HCC has been shown to be reduced after antiviral therapy. However, few cases of HCC in patients with chronic hepatitis C are still reported even after antiviral treatment. This study investigates the risk of developing HCC in chronic hepatitis C carriers after antiviral therapy. It aims to identify population with high risk of HCC occurrence and to confirm the protective role of SVR. The major endpoint is to define predictors of developing HCC after achieving SVR. We'll try to present suggestions about screening strategies (indications and interval) after antiviral therapy according to level of HCC occurrence risk.

Patients and methods

It's a monocentric, retro-prospective and analytic study. It includes all patients with chronic hepatitis C enrolled in our department from January 2002 and April 2010, who were considered for antiviral treatment. At study onset, included patients had no HCC and they were not co-infected by hepatitis B or HIV. They were all tested for HCC before inclusion: abdominal ultrasonography was systematically performed prior to antiviral therapy. Patients with current or previous history of HCC were excluded. All participants were treated by Peg-IFN/RBV. During the follow-up, all patients benefited from ultrasonography biannually after treatment to detect suspected hepatic nodules.
Diagnosis of HCC was retained on the basis of histological confirmation when biopsy was performed or according to morphological non invasive criteria (Barcelona criteria) for cirrhotic patients where biopsy was not necessary. For each patient, we considered following metadata: age at HCV diagnosis, gender, baseline viral loads (BVL), Hepatitis C genotype, necro-inflammatory activity (A) and fibrosis (F) degrees at the beginning of antiviral treatment. Histological activity and fibrosis were evaluated according to METAVIR score (F >2 was considered as an advanced stage of fibrosis). We considered initially all treated patients regardless of treatment outcome and we compared treated patients who didn't develop HCC at the follow-up to patients who developed HCC; we used khi-2 and Ficher-Exact analysis. In a second step, we were particularly interested in the population of patients who developed HCC even they achieved SVR in order to elucidate the risk factors of developing HCC after SVR. We compared sustained virological responders who didn't develop HCC to sustained virological responders with developed HCC in the follow-up. we used Pearson chi-square test. Patients included in this study had at least **03** years of regular biannual follow-up.

Results:

Three hundred sixty nine patients received antiviral treatment for hepatitis C in our department from January 2002 to April 2010 and were then included in our study. Time of follow up ranges between 3 and 9 years with a median of 6 years. During the regular bi-annual follow up, 20 HCC has been diagnosed which corresponds to 5% of previously treated population. In the 20 participants who developed HCC, 12 were female (60%) and 8 male (40%); the mean age was 61 years old [40- 72]. The mean time for HCC occurrence was 5 +/-2 years. Fifty Tree percent of patients had a HCV- genotype 1 (HCV- 1) and 47% had HCV-genotype 2 (HCV-2). Ninety five percent presented severe fibrosis at the beginning of treatment (Table I). SVR was achieved in 259 patients (70%). In patients with SVR, only 06 of 259 developed HCC (2. 3%) fig. 1.
Considering all treated population, the comparison of HCC occurrence rate in patients who didn't achieve SVR to sustained virological responders shows significant results: HCC was reported in 2.3% of sustained virological responders vs. 12.5% of non-SVR patients (p=0.004) (Fig. 1) which confirms that SVR reduces significantly the risk of developing HCC. The risk of HCC development was not significant according to patients gender and Hepatitis C genotypes (respectively p= 0.63 and p=0.87). Advanced age at diagnosis and severe fibrosis were significant risk factors (respectively p=0.003 and p= 0. 0001) (Table II).
Of the 20 patients who developed HCC, six were previously sustained virological responders. They

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Research Article
ISSN: 2351-8200
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were 3 male and 3 female. Mean age was **60** years old [51- **70**]. **Five** patients had HCV- 2 and only one had HCV- 1. Fibrosis stage was severe (F3-F4) in all patients. The risk of HCC occurrence in sustained virological responders was not significantly associated to gender, genotypes and initial high viral loads (respectively **p=1**, **p=0.4** and **p=0.57**). High necro-inflammatory activity (A) didn't influence hepatocarcinogenesis. Severe fibrosis was the only significant risk factor of developing HCC after achieving SVR (**p=0.01**) (Table III).

Table I: General features of HCV- treated patients who developed HCC.

*Total study population	369
*Number of patients who developed HCC	20
*Gender -Male	08
- Female	12
*Mean age (years old)	61
*Mean time of HCC occurrence (years)	5+/-2
*HCV genotypes	
-HCV-1	53%
-HCV-2	47%
*Fibrosis (METAVIR score)	94.6%
-Severe	5.4%
-reduced	
*Response to antiviral treatment	
-Sustained virological responders	06
-Non-SVR patients	14

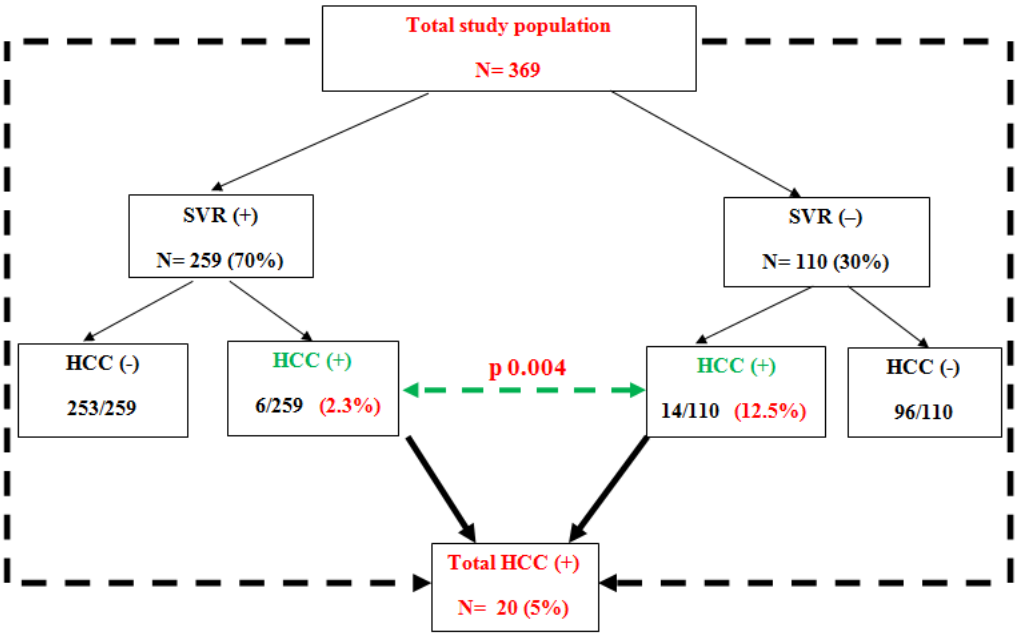

Fig.1: Achieving SVR reduces significantly the risk of HCC development (p= 0.004)

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Table II: predictors of developing HCC in treated HCV carriers

		n (%)	P
Gender	Male Female	148 (40%) 221 (60%)	p=0.63
Age of initial diagnosis of HCV	> 60 y.o ≤ 60y.o	277 (75%) 92 (25%)	p=0.003
Genotype	Genotype 1 Genotype 2	196 (53%) 173 (47%)	p=0.87
Initial fibrosis	F1-F2 F3-F4	18 (5%) 351 (95%)	p= 0.0001
Treatment Response	SVR achieved non achieved SVR	118 (32%) 251 (68%)	p= 0.004

Table III: Advanced fibrosis is the only significant risk factor of HCC development after achieving SVR.

		Patients with developed HCC		Patients with no HCC	P
Gender	Male	3.3%	Vs.	96.7%	p=1
	Female	3.4%	Vs.	96.6%	
Age of diagnosis	Age≤55	1%	Vs.	99%	p=0.1
	Age>55	5.7%	Vs.	94.3%	
HCV Genotypes	1	1.3%	Vs.	98.7%	p=0.4
	2	4.7%	Vs.	95.3%	
Baseline viral loads (BVL)	High BVL	3%	Vs.	97%	p=0.57
	Low BVL	1.1%	Vs.	98.9%	
Necro inflammatory activity	A≤2	3.2%	Vs.	96.8%	p= 0.4
	A>2	6.3%	Vs.	93.7%	
Fibrosis****	F≤2	0%	Vs.	100%	p=0.01
	F>2	8.8%	Vs.	91.2%	

Discussion

Hepatitis C is a real public health problem worldwide. It's an oncogenic virus with a particular tropism for the liver and a well-known etiology of HCC. In Morocco, according to recently conducted meta-analysis of the epidemiology of Hepatitis C in the Maghreb region, the National prevalence of Hepatitis C in general population was estimated to 0.8% (95%CI: 0.5–1.2) [4]. In a National cross-sectional survey among 41269 participants, the overall prevalence of HCV infection in the general population was found to be 1.58% [5]. In other hand, prevalence was estimated to 74% and 44% in individuals with chronic or acute hepatitis [4, 6]; a Moroccan study interested in a selected population of patients with HCC reported a prevalence rate of 57% [4, 7].

Each year, HCC is diagnosed in more than half a million people worldwide, including approximately 20.000 new cases in the United States [8]. Risk factors for HCC include infection with hepatitis B or C, alcoholic liver disease, nonalcoholic fatty liver disease and exposure to environmental toxins especially aflatoxine. In the North Africa, despite of the high prevalence of HBV infection, HCC development seems to be more associated with hepatitis C than hepatitis B [9]. It's known in the HVC infection's natural history that 20% of infected patients will develop severe chronic hepatitis C and cirrhosis which is considered as a precancerous condition predisposing to HCC [10, 11]. The HCV-induced HCC development is a multi-step process that creates persistent chronic hepatic inflammation, progressive fibrogenesis in the hepatocysts, initiation of neoplastic clones accompanied by irreversible somatic genetic/epigenetic alterations, and progression of the malignant clones in a carcinogenic tissue microenvironment [**3**]. This process could take 20–40 years.

The great advantage in the management of chronic hepatitis C compared to hepatitis B is that Hepatitis C virus can be completely eradicated after treatment. Indeed, antiviral therapy of chronic hepatitis C has been developed rapidly and, in thirty years, SVR rates increased from 6% to up to 90%. Actually, after introducing DAA drugs, it's established definitively that Hepatitis C is a curable infection.

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Journal of Medical and Surgical Research
Research Article
ISSN: 2351-8200
JMSR 2016, Vol III; N°1: 223- 228

The new drugs, that can be combined to provide short and well tolerated all oral regimens, allows high rates of SVR for all HCV genotypes even in patients previously considered "difficult-to-treat" and in patients with advanced cirrhosis that in the past were contraindicated to antiviral treatment. [12]
Our study was interested in the outcome of HCV carriers who benefited of antiviral therapy; in our series, antiviral treatment was the association Peg-IFN/RBV which has been retained for long time as standard of care in HCV-chronically-infected patient. The major assessment was that HCC may occur in treated patients even if SVR has been successfully achieved.
The predictors of HCC occurrence in treated HCV carriers were advanced age (> 50 years old), severe fibrosis and lack of SVR. Our study suggests that older patients -over 50 years old- were a risk factor population for HCC occurrence after antiviral treatment. This was reported by Nihon Rinsho who showed that the risk for developing HCC depends on age and is more important after 65 years-old [13]. Furthermore, it was demonstrated that the benefit of HCV eradication on HCC prevention was less significant in older patients than in younger [13].
Our patients with severe fibrosis were the second risk factor population; it's established in the literature data that the risk of HCC gradually increases as liver fibrosis progresses. Once cirrhosis is established, the annual incidence of HCC is extremely high (1–7% per year), although HCC rarely develops in less fibrotic livers [3, 14] .
Finally, the protective role of SVR [3] has been demonstrated again in our series. The lack of SVR exposes significantly to HCC development. Continuing biannual regular screening of HCC in non-responders patients is the rational strategy. Some authors suggest that the lack of surveillance after SVR was obviously associated with more advanced HCC at detection, resulting in poor prognosis. In addition, there is a difference in the severity of HCC at diagnosis according to the surveillance interval [3].
It's certain that achieving SVR improves the prognosis of patients and limits fibrosis progression which reduces the risk of HCC development. This preventive effect may be explained by the anti-inflammatory effect of stopping necro-inflammatory mechanisms responsible of progression of fibrosis in the previously infected liver. However, HCV eradication does not abolish definitely the risk of HCC [15]. In our series, 2.3% of sustained virological responders developed HCC: the previous carcinogenic effects of HCV proteins may continue to create a cellular tissue microenvironment that serves to tumor evolution even after virus eradication. This demonstrates that screening is still indicated even after SVR! This founding led to the big question of screening strategy (surveillance interval, surveillance duration and high risk population) after SVR. If we established that screening is indicated even after SVR, should we process with bi-annual ultrasonography screening even if fibrosis stage is reduced (F1- F2)?
Actually, regression of cirrhosis is now a recognized concept [16, 17]. Liver fibrosis has been defined as a dynamic and potentially bidirectional process and the spontaneous regression of fibrosis has been demonstrated in both animal models of hepatic fibrosis and human trials in which the responsible agent of chronic hepatitis has been successfully controlled, like SVR condition [16]. In the coming decades, regression of cirrhosis should become the secondary reasonable goal after inactivation of viral hepatitis C [17]. HCV infection is associated with a 15- to 20-fold increase in risk for HCC compared with HCV-negative subjects in cross-sectional and case-control studies [18]. This could suggest that patients with reduced fibrosis at HCV diagnosis, who achieved SVR after antiviral therapy, present a lowest risk for developing HCC. The interval of regular screening in those patients could be reduced to annual surveillance only.
One of our study's endpoints was to define risk factors of HCC occurrence in sustained virological responders to define the profile of patients who should be carefully and closely considered for HCC screening after SVR. In our series, all the sustained virological responders who developed HCC had an advanced fibrosis stage (F>2 according to Metavir Score) and it has been shown statistically that this condition is the only significant risk factor for developing HCC after achieving SVR.
Establishing guidelines about consensual strategy to survey sustained virological responders is necessary. If it's clearly estabilished that regular bi-annual screening is indicated in patients with advanced fibrosis stage even more when co-morbid conditions are associated (such as older patients, diabetes mellitus, nonalcoholic fatty liver disease, alcoholism…), it becomes strongly important to stay about the surveillance strategy in the other patients categories. We are now in the era of anti-viral drugs associated to higher SVR rates; also, HCV therapy is indicated today in patients with reduced fibrosis as a major element of the global vision for HCC prevention and HCV eradication worldwide.

Conclusion

In our series, 5% of previously treated HCV carriers developed HCC and 2.3% of sustained virological responders developed. Our results confirm the evidence that achieving SVR after antiviral therapy

ISSN: 2351-8200
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is a protective factor which decreases significantly the incidence of HCC in patients with HCV. Advanced age (> 50 y. o) severe fibrosis (F>2) and lack of SVR at HCV diagnosis are predictive factors of HCC development in treated patients. According to our real-life experience, regular bi-annual ultrasonography screening should be indicated necessarily in patients with advanced fibrosis stage (F3- F4) even after SVR, particularly when co-morbid conditions are associated (advanced age, NASH, diabetes mellitus,…). Screening interval in sustained virological responders with reduced fibrosis stage may be reduced to annual surveillance. Establishing guidelines about consensual strategy to survey sustained virological responders is now necessary especially with high rates of SVR and the extension of treatment indications in era of DAA drugs.

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