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The risk of early occurrence and recurrence of hepatocellular carcinoma in hepatitis C infected patients treated with direct acting antivirals with and without Pegylated Interferon: A Belgian experience.

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ABSTRACT

Introduction

Recently, concerns were raised of high rates of HCC recurrence in patients treated with direct acting antivirals (DAA) for hepatitis C infection. We investigated the HCC occurrence and recurrence rates within six months after treatment with DAA with or without Pegylated Interferon (PEG-IFN) in real life.

Methods and materials

This is a retrospective, multicenter cohort trial, executed in 15 hospitals distributed across Belgium. Populations were matched based on fibrosis score (Metavir F3-F4). Patients with a Child-Pugh score ≥ B were excluded. In total, 567 patients were included, of whom 77 were treated with PEG-IFN+DAA between 2008 and 2013 and 490 with DAA without PEG-IFN between 2013 and 2015.

Results

Patients treated with PEG-IFN+DAA (53±9y) were younger than patients treated with DAA without PEG-IFN (59±12y) (p=0.001). 47% of patients treated with PEG-IFN+DAA were in the F4 stage versus 67% of patients treated with DAA without PEG-IFN (p=0.001). Screening was inadequate in 20% of both patient groups (p=0.664). The early occurrence rate of HCC was 1.7 % and 1.1% in patients treated with DAA with and without PEG-IFN respectively (p=0.540). The early recurrence rate was 0% in patients treated with PEG-IFN+DAA, and 15.0% in patients treated with DAA without PEG-IFN (p=0.857).

Conclusion

There is no difference in early occurrence of new HCC between patients treated with DAA with and without PEG-IFN. We did observe a high early recurrence rate of HCC in patients treated with DAA without PEG-IFN. However, these patients were at baseline more at risk for HCC. Finally, in 20% screening for HCC was inadequate.

KEYWORDS

Direct acting antiviral therapy, hepatocellular carcinoma, hepatitis C, pegylated interferon

INTRODUCTION

Patients with cirrhosis whether or not caused by hepatitis C viral infection (HCV) are at risk for development of hepatocellular carcinoma (HCC).(1, 2) Multiple studies have provided evidence that achieving a sustained viral response (SVR) is associated with a reduced risk of HCC.(3-11) Nevertheless, the risk of HCC persists also after SVR and continued monitoring is necessary.(9) Especially patients with cirrhosis, older patients and patients with diabetes, the risk of HCC is estimated to be higher.(9, 12, 13)

The introduction of direct acting antiviral therapy (DAA) has revolutionized HCV therapy these last years.(14-17) These regimens are highly effective and with the arrival of new pan-genotypic regimens in the near future, nearly 100% of the patients can be cured with even more simplified regimens.(18-21) However, caution has been raised for high rates of HCC occurrence and recurrence in patients treated with DAA.(22-25) This heightened the discussion regarding the use of DAA in high-risk patients.(26, 27) However, a retrospective study of three distinct cohorts (HEPATHER-, CirVir- and CUPILT-cohort) of 660 patients in total of whom 516 received DAA therapy, did not report an increased risk of HCC recurrence after DAA treatment.(28)

Therefore, the evidence is still unclear whether there is a real increased risk of HCC after DAA treatment. We have performed a retrospective analysis of patients treated with DAA with and without pegylated interferon (PEG-IFN) in order to further investigate the link between HCC recurrence or occurrence and DAA therapy.

METHODOLOGY

Study Design

We performed a national, retrospective cohort study in 15 hospitals, distributed across Belgium. Data were available from two studies which used the same methodology, focusing on the outcome of DAA with and without PEG-IFN in HCV infected PWID vs non-PWID.(29, 30) Data were collected from the medical patient files.

From the first study, all patients treated with PEG-IFN + ribavirin + telaprevir or boceprevir with a fibrosis score of a Metavir-score of F3/F4 were included. Data were collected between between 2008 and 2013 in 11 hospitals. From the second study, all patients treated with simeprevir + sofosbuvir ± ribavirin, daclatasvir + sofosbuvir ± ribavirin or ombitasvir/paritaprevir ritonavir – dasabuvir ± ribavirin were included. As the Belgian reimbursement criteria were applicable on all these patients, this cohort existed of patients with F3-F4 fibrosis only. Patients with child-pugh B and C cirrhosis were excluded. Data were collected between December 2013 and December 2015 in 15 hospitals.

Endpoints of study

The main objective of this trial was to compare the occurrence and recurrence rates of HCC in patients treated with DAA with and without PEG-IFN. As a secondary objective, we analyzed the percentage of patients who have received radiological follow up within six months after DAA therapy.

Study population

In total, 567 patients were included in this study: 77 patients were treated with DAA and PEG-IFN and 490 were treated with DAA alone. From the patients treated with PEG-IFN, 55.8% (n=43/77) were treated with peginterferon + ribavirin + telaprevir, and 44.2% (n=34/77) were treated with peginterferon + ribavirin + boceprevir. From the patients treated with DAA, 56.1% (n=275/490) patients were treated with simeprevir + sofosbuvir ± ribavirin, 35.1% (n=172/490)

with daclatasvir + sofosbuvir ± ribavirin and 8.8% (n=43/490) with ombitasvir/paritaprevir ritonavir – dasabuvir.

Statistical analysis

Descriptive statistics of patient characteristics are presented: for continuous variables, means and standard deviation, for categorical variables proportions and percentage are given. To compare patient groups, regression methodology was used for continuous variables (such as age and BMI), and Chi-square test for categorical variables (such as fibrosis score, treatment completion). A P-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Patient characteristics are described in Table 1. Patients treated with DAA without PEG-IFN were significantly older and were more often in a compensated cirrhotic stage. They had a different genotype distribution as therapy with PEG-IFN + telaprevir or boceprevir was only reimbursed for genotype 1 patients in Belgium. 51/77 patients treated with PEG-IFN + DAA (66.2%) reached SVR versus 452/479 (94.4%) of the patients treated with DAA without PEG-IFN.

The characteristics of HCC staging and treatment are described in Table 2. Most patients had a BCLC stage A score, and the median follow time between the treatment for HCC and start of HCV treatment was 12 months. Data of the follow-up time were prone to large outliers of patients in follow-up for more than 10 years. 17 patients had follow up of less than 1 year.

Results of follow-up:

The results of follow-up for HCC are visualized in figure 1. In both groups, 80% of patients were screened for HCC by radiological follow-up at least 6 months after the end of treatment for HCV. There was a low rate of HCC occurrence within six months after treatment of 1.1% (n=4/355) in the group treated with DAA and 1.7% (n= 1/59) in the group treated with PEG-IFN + DAA. HCC recurrence however was high in the group treated with DAA without PEG-IFN: 15% (n=6/40).

Characteristics of the patients with HCC recurrence and HCC occurrence are provided respectively in Table 3 and 4. Patients with HCC in the patient history (64±9y) were clearly older than patients without HCC in their history (58±12y) (p=0.001). Both patients with HCC recurrence and occurrence had a lower rate of SVR. However, this was biased as 4/5 patients who did not reach SVR in these patient groups actually developed HCC during the DAA treatment. This was a reason to stop treatment in these patients. Furthermore, patients with a HCC recurrence, were treated by liver resection (LR) or radiofrequency ablation (RFA) for their primary HCC. This differs significantly from the patients without recurrence: 22 of these patients were treated by a liver transplantation and no patients who had a liver transplant had a recurrence.

DISCUSSION

Due to the development of DAA, our ability to treat HCV infected patients has increased significantly, and more difficult to treat patients can be cured.(18, 21, 31, 32) Earlier trials in the interferon era have provided evidence that reaching sustained viral response (SVR) significantly

improves patient outcome, with less development of decompensated cirrhosis and HCC.(3-11) However, this has not been shown for patients treated with DAA, as long-term follow-up is not yet available for these patients. Recently, questions were raised regarding higher than expected recurrence rates of HCC in patients treated with DAA.(22, 23) This conclusion was not confirmed in a retrospective evaluation of patients with HCC in three large cohorts.(28) Furthermore, not only recurrence rates were estimated to be higher, but two more trials warned for higher than expected occurrence rates.(24, 25)

We investigated the occurrence and recurrence rates in a large, multicenter, real-life cohort. To compare this to the interferon era, only patients with a fibrosis stage of F3 or F4 (Child-Pugh A) were included. This was based on the reimbursement criteria for DAA in Belgium, and on the treatment paradigm in the interferon era to not treat patients with advanced liver disease.

In our cohort, we could not find higher than expected early occurrence rates of HCC in patients treated with DAA without PEG-IFN (1.1%; n=4/355) vs. people treated with PEG-IFN + DAA (1.7%; n=1/59). These rates were comparable to the estimated 1%/year frequency of HCC in patients with SVR treated with PEG/IFN and ribavirin dual therapy.(33-36)

We did find a high recurrence rate of 15.0% (n=6/41) six months after treatment with DAA without PEG-IFN. We could not compare this to the cohort of patients treated with PEG-IFN + DAA, as only 1 patient was treated who had a HCC in the history. In our cohort, we found that patients with a HCC recurrence also had a lower SVR rate, but this was due to development of HCC even during treatment. This was the reason to stop treatment in a palliative setting for two out of three patients. Importantly, only patients treated by LR or RFA of the primary HCC developed recurrence, whereas patients with a liver transplantation did not. Thus 33.3% (3/9) of patients treated with LR had a recurrence and also 33.3% (3/9) of the patients treated with RFA. The time interval from treatment of HCC to treatment of HCV was 10±9 months in the group treated by LR (after removal

of one statistical outlier with an interval of 247 months), versus 14±11 months in the group treated by RFA. The time to recurrence interval was 17±12 months in the group treated by LR and 25±4 months in the group treated by RFA. Early HCC recurrence (<2years) complicates 26-50% of the patients treated by LR and 2-18% of the patients treated by RFA.(37-41) Thus, although we found a high early recurrence rate after DAA treatment, these rates are comparable to the findings of the outcome of HCC recurrence after LR or RFA after 24 months of follow-up. Therefore, we cannot state that there is a direct effect of DAA treatment to the HCC recurrence rates in our cohort. Nevertheless, HCC occurrence or recurrence remains a possibility, therefore clinicians must remain vigilant, also after achieving SVR. This was important in the interferon-era, and will remain important in patients treated with DAA.(33-36). In this real-life cohort, follow up rates were not ideal, as 20% of the people are not screened by radiographic (ultrasound/CT or MRI) analysis at least six months after the end of treatment. Therefore, it is imperative to inform clinicians and patients that a risk of developing HCC remains even after the cure of HCC, and regular follow up is necessary.

CONCLUSION

There is no difference in early occurrence of new HCC between patients treated with DAA with and without PEG-IFN. We did observe a high early recurrence rate of HCC in patients treated with DAA without PEG-IFN. However, recurrence was only seen in patients treated by LR and RFA, and recurrence rates were similar to the rates in patients treated with these treatments after 24

months. In 20%, screening for HCC was inadequate. More efforts are necessary as we need to remain vigilant when treating high risk patients.

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TABLES

Table 1: Differences in patient characteristics between patients treated with DAA with and without PEG-IFN.

	PEG-IFN + DAA (n=77)	DAA (n=490)	p-value
Age (y)	52 ± 9	59 ± 12	**0.001**
Gender			0.161
- male	55 (71.4%)	307 (62.7%)	
- female	22 (28.6%)	183 (37.3%)	

BMI (kg/m²)	27.2 ± 4.6	26.3 ± 4.5	0.169
Comorbidity			
- Diabetes	14/76 (18.4%)	94/490 (19.2%)	0.878
- Renal insufficiency	6/73 (8.2%)	34/490 (6.9%)	0.629
- Psychiatric comorbidity	17/77 (22.1%)	129/485 (26.6%)	0.485
- Liver transplantation	3/73 (4.1%)	33/490 (6.7%)	0.392
Substance abuse			
- Ethyl	16/75 (21.3%)	61/490 (12.4%)	**0.046**
- Injection drug use	27/77 (35.1%)	100/490 (20.4%)	**0.008**
HBV coinfection	1/72 (1.4%)	1/403 (0.2%)	0.280
HIV coinfection	4/76 (5.3%)	35/416 (8.4%)	0.489
HCC	1/77 (1.3%)	41/490 (8.4%)	**0.031**
Treatment experienced	41/77 (55.8%)	285/487 (58.5%)	0.710
HCV Genotype			**0.001**
- 1a	29/76 (38.2%)	97/489 (19.8%)	
- 1b	42/76 (55.3%)	234/489 (47.9%)	
- 1 (other)	5/76 (6.6%)	11/489 (2.2%)	
- 2	-	-	
- 3	-	69/489 (14.1%)	
- 4	-	72/489 (14.7%)	
- 5	-	2/489 (0.4%)	
- 6	-	-	
- Mixed	-	4/489 (0.8%)	
Viral load (IU/ml)	2.225.788 ± 2.242.795	2.010.473 ± 2.167.505	0.381
Fibrosis stage			**0.001**
- F3	41/77 (53.2%)	160/486 (32.9%)	
- F4 (Child-Pugh A)	36/77 (46.8%)	326/486 (67.1%)	
SVR	51/77 (66.2%)	452/479 (94.4%)	**0.001**

PEG-IFN: pegylated interferon; DAA: direct acting antiviral therapy; BMI: body mass index; Psychiatric comorbidity: history of depression, psychosis, anxiety or schizophrenia; Ethyl: > 2-3 alcoholic beverages per day; Injection drug use: patients who have ever injected drugs; HCV: hepatitis C viral infection. HBV: hepatitis B viral infection; HIV: human immunodeficiency virus. HCC: history of hepatocellular carcinoma. Fibrosis stage: according to Metavir criteria. If F4 stage: Child-Pugh classification was used. SVR: sustained viral response.

Table 2: HCC characteristics before HCV treatment

	PEG-IFN + DAA (n=1)	**DAA (n=41)**
BCLC staging score		
- 0	-	1/41 (2.4%)
- A	1/1 (100%)	33/41 (81.0%)
- B	-	7/41 (17.1%)
Volume HCC (cm)	1.9	3.31 ± 3.17
Number of tumors (n)	1	1.53 ± 0.76

Alpha-fetoprotein level (IU/ml)	14.3	45.6 ± 69.7
Treatment		
- Liver transplantation	1/1 (100%)	21/41 (51.2%)
- Resection	-	10/41 (24.4%)
- RFA	-	9/41 (22.0%)
- TACE	-	1/41 (2.4%)
Mean time between HCC treatment and start HCV treatment (months) (mean ± SD; median)	11 months	33 months ± 47; 12

BCLC= Barcelona clinic liver cancer (group); Volume HCC: largest diameter of largest nodule; number of tumors: number of HCC localizations in the liver; alpha-fetoprotein level: level of alpha-fetoprotein before treatment for HCC; RFA= radio-frequency ablation; TACE= trans-arterial chemo-embolization.

Table 3: Characteristics of patients with HCC recurrence vs patients without HCC recurrence 6 months after DAA treatment.

	HCC recurrence (n=6)	**Non-HCC recurrence (n=35)**	**P-value**
Age (y)	65 ± 12	64 ± 9	0.868
BMI (kg/m²)	28.1 ± 5.2	25.9 ± 4.3	0.362
Diabetes	4/6 (66.7%)	15/35 (42.9%)	0.512
Fibrosis stage			0.559

- F3	1/6 (16.7%)	8/32 (25.0%)	
- F4 (Child-Pugh A)	5/6 (83.3%)	24/32 (75.0%)	
SVR	3/6 (50.0%)	33/35 (94.3%)	**0.017**
BCLC staging			0.914
- 0	-	1/35 (2.9%)	
- A	5/6 (83.3%)	28/35 (80.0%)	
- B	1/6 (16.7%)	6/35 (17.1%)	
Volume (cm)	2.9 ± 1.3	3.5 ± 3.7	0.661
Number of tumors (n)	1.17 ± 0.4	2.0 ± 2.11	0.346
Alpha-fetoprotein level (IU/ml)	63.32 ± 89.73	43.40 ± 68.02	0.582
Time interval (months) (mean ± SD; median)	16 ± 10; 17	35 ± 50; 12	0.381
Treatment HCC			**0.009**
- Liver transplantation	-	22/35 (62.9%)	
- Resection	3/6 (50.0%)	6/35 (17.1%)	
- RFA	3/6 (50.0%)	6/35 (17.1%)	
- TACE	-	1/35 (2.9%)	
Time to recurrence HCC (mean ± SD; median)	21 ± 11; 24	-	

BMI= body mass index; SVR= sustained viral response; BCLC= Barcelona clinic liver cancer (group); Volume HCC: largest diameter of largest nodule; number of tumors: number of HCC localizations in the liver; alpha-fetoprotein level: level of alpha-fetoprotein before treatment for HCC (after removal of outlier of 2321IU/ml in the non-HCC recurrence group); Time interval= time between HCC treatment and start HCV treatment; SD= standard deviation: HCC= hepatocellular carcinoma; RFA= radiofrequent ablation; TACE= transarterial chemo-embolization.

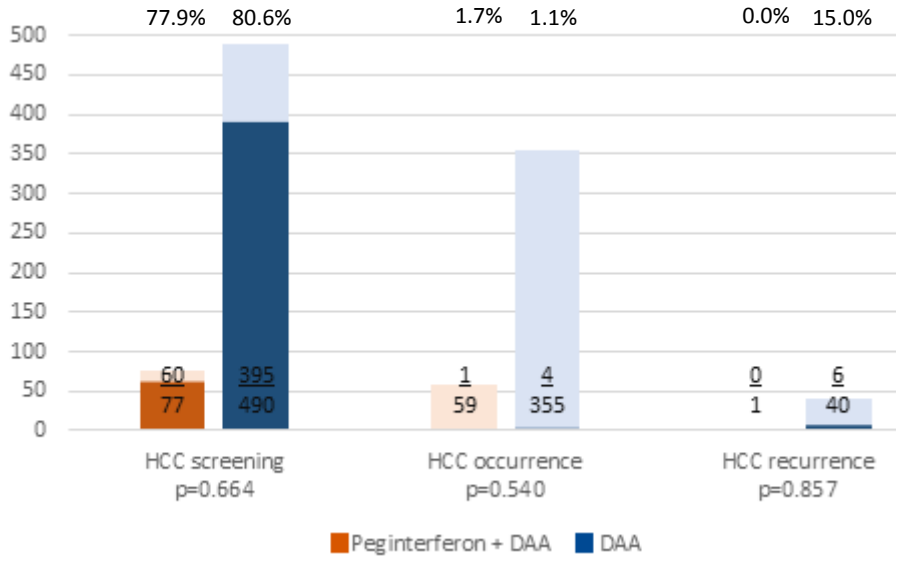
Table 4: Characteristics of patients with HCC occurrence vs patients without HCC occurrence six months after DAA treatment.

	HCC occurrence (n=5)	**Non-HCC occurrence (n=409)**	**P-value**
Age (y)	62 ± 9	58 ± 12	0.451
BMI (kg/m²)	31.3 ± 8.9	26.5 ± 4.3	0.365
Diabetes	2/5 (40.0%)	78/408 (19.1%)	0.249
Fibrosis stage			0.449
- F3	1/5 (20.0%)	139/408 (34.1%)	
- F4 (Child-Pugh A)	4/5 (80.0%)	269/408 (65.9%)	
SVR	3/5 (60%)	369/407 (90.7%)	0.076

HCC= hepatocellular carcinoma; BMI= body mass index; SVR= sustained viral response.

FIGURES

Figure 1: Screening, occurrence and recurrence rates of HCC in patients treated with DAA with and without PEG-IFN.



HCC= hepatocellular carcinoma; DAA= direct acting antiviral therapy.