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Chronic Viral Hepatitis C: Before and after Direct Acting Antivirals (DAA) in Morocco

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Abstract

For a long time, a combination of interferon and ribavirin has been used to treat viral hepatitis C, but the sustained virological response was only achieved in 45% of cases and side effects were serious [1]. Direct acting antivirals (DAA) have provided a cure for almost everyone with hepatitis C, with few side effects. **The Purpose of Our Work** is to compare the results of treatment for viral hepatitis C before and after DAA. **Patients and Methods:** This is a retrospective study, bringing together all patients with chronic viral hepatitis C treated between January 2009 and March 2020 at the University Hospital Hassan II in Fez, Morocco. The epidemiological, clinical, biological, virological characteristics of the included patients were collected from the two groups: A, treated with interferon and ribavirin or by triple therapy and B, treated with DAA. **Results:** 162 patients were included, the average age was 55 y/o, with 90 women and 72 men. 88 patients (54.3%) were already cirrhotic, of which 61 were compensated and 27 were decompensated. Genotype 1 was dominant with a frequency of 71.6%, 107 patients (66%) initially treated with old HCV treatments and 55 (34%) treated with DAA. Sustained viral response was obtained in 59 cases (55.14%) in group A versus 54 cases (98.18%) in group B with a very significant difference ($p < 0.0001$). Treatment failure was observed in 14 patients (13.1%) in group A and only one patient, *i.e.* 2% in group B ($p = 0.019$). 14 patients relapsed in group A (13.1%) versus 0 patient in group B ($p = 0.003$). The tolerance of the treatment was excellent in group B as a whole with only five patients (9%) reported side effects which were minor, not leading to the discontinuation of treatment while the side effects were major in 49 patients (45.7%) in group A with led to the permanent discontinuation of treatment in 6 patients. The difference in side effects be-

tween the two groups was very significant with ($p < 0.0001$). **Conclusion**: Our study has shown the superiority of DAA in terms of efficacy and tolerance compared to the old treatments for chronic hepatitis C. In addition, these treatments allow almost systematic viral elimination and therefore consequently a reduction in the risk of complications hepatic with a short time of treatment.

Keywords

Viral Hepatitis C, Pegylated Dual Therapy, Direct Acting Antivirals, Tolerance

1. Introduction

Hepatitis C is a viral infection mainly transmitted through the blood. It can remain asymptomatic for a long time and in 80% of cases progresses to chronic hepatitis. Hepatitis C can sometimes be diagnosed during targeted screening: blood donation, pregnancy or investigation after suspected contact with the virus by testing for anti-HCV antibodies (serology) using a simple blood test. After diagnostic confirmation, physical examinations are necessary to assess the severity of liver disease, mainly Fibroscan. Its main screening aims to offer treatment to infected people. While it has long relied on the combination of pegylated interferon and ribavirin, HCV treatment has experienced rapid and dramatic development over the past six years. The development of fast-acting, non-immune mediated antivirals is behind these rapid advances. This development is arousing great interest among practitioners and their patients with the hope of more effective and better-tolerated therapies with a cure rate exceeding 95%. These treatments aim to eradicate HCV, to prevent, stabilize or reduce lesions. of the liver, and to prevent complications such as cirrhosis or cancer of the liver from developing. They should also ultimately reduce the number of new cases of people with hepatitis C. The purpose of our work is to study the results of treatment of viral hepatitis C with and without DAA.

2. Patients and Methods

This is a retrospective study, collecting all patients with HCV treated between January 2009 and March 2020. Efficacy and safety were evaluated in the two groups treated with interferon and ribavirin or tritherapies type telaprevir Group A: GA) and those treated with DAA (Group B: GB). Data analysis was done by SPSS software and a $p < 0.05$ is considered significant.

3. Results

During the period between January 2009 and March 2020, 162 patients were included. The mean age was 55 y/o with extremes of 33 y/o to 82 y/o, divided into 90 females and 72 males. The clinical manifestations were mostly asthenia and

arthralgia. 54.3%were already cirrhotic, of which 61 were compensated and 27 were decompensated (12 hemorrhagic decompensations; 10 ascitic decompensations and 5 decompensated by hepatic encephalopathy). Genotype 1 was dominant with a frequency Of 71.6%, followed by genotype 2 in 45 patients (27.2%) and a combination of genotypes 1 and 4 in only 1 patient (0.6%). 107 patients (66%) were treated in the first line with the previous HVC treatments and 55 (34%) with DAAs. The most frequently proposed regimens due to their availability in Morocco were sofosbuvir (SOF)/Daclatasvir (DAC) ± Ribavirin (RBV) in 47 patients (85.45%) followed by (SOF)/ledipasvir (LDV) ± ribavirin (RBV). 40 patients were treated for 12 weeks and the remaining 15 for 24 weeks. Sustained viral response was obtained in 59 cases (55.14%) in group A versus 54 cases (98.18%) in group B with a very significant difference ($p < 0.0001$), and treatment failure in 14 (13.1%) in group A versus only one or 2% in group B ($p = 0.019$), Relapse was observed in 14 cases (13.1%) versus 0 cases in group B ($p = 0.003$) (Table 1).

In group A, 49 patients were cirrhotics versus 58 non-cirrhotics. In group B, 36 patients were cirrhotics versus 15 non-cirrhotics and the difference in terms of remission; failure and relapse were not significant. Regardless of the prescribed therapeutic regimens, sustained viral response was observed in 64.77% in the cirrhotic group versus 66.2% in the non-cirrhotic group ($p = 0.565$), treatment failure was noted in 12.5% in the cirrhotic group versus 5.4% in the non-cirrhotic group ($p = 0.091$), and relapse was observed in 9% of the cirrhotic group versus 8% in the non-cirrhotic group ($p = 0.509$). We can conclude that cirrhosis is an independent factor in hepatitis C treatment failure regardless of the prescribed therapeutic regimens. 16 cirrhotic patients (18.18%) developed hepatocelullar carcinoma (HCC) versus 1(1.38%) in non-cirrhotics with ($p = 0.007$).

Table 1. Characteristics of group A and B.

	Group A	Group B	p
Number of patients	107	55	
Average Age	50	47	0.15
Sex	60F/47H	30F/25H	0.45
Genotype	G1: 76 G2: 31	G1: 40 G2: 14 G1 et 4: 1 case	
Cirrhosis	49	36	0.5
Viral load	455,233 UI/ML	400,034 UI/ML	0.66
Sustained viral response rate	59% or 55.14%	54% or 98.18%	$p < 0.0001$
Failure rate	14% or 13.1%	1% or 2%	$p = 0.019$
Relapse rate	14% or 13.1%	0%	$p = 0.003$
Side effects	Anemia; thrombocytopenia; pancytopenia; diarrhea; vomiting; anorexia; asthenia; sleep disorders; dementia syndrome; seizure disorder; depressive syndrome	Vomiting; nausea Myalgias; asthenia	
Tolerance	45.7%	9%	$p < 0.001$

Among the cirrhotic patients who developed HCC, 5 patients were not yet treated for their HCV; 8 patients treated with pegylated dual therapy with a mean delay of 4 years (1 and 10 years); 2 patients treated with pegylated dual therapy with treatment failure and only 1 patient treated with Sofo + Dacla type DAAs in the first month of treatment. We also noted that among the cirrhotic patients treated for HVC, 64 (73%) of the patients have kept the same Child score, with worsening of the Child score in 3 (3.40%) patients and improvement of the Child score in 21 (24%) patients with a mean of 2 points ($p = 0.003$). The mortality rate in our series was estimated at N = 14 (8.6%) of which 12 were cirrhotic and 2 non-cirrhotic with ($p < 0.0001$).

Tolerance was excellent in all of Group B, with only five patients (9%) reporting minor adverse events (asthenia, myalgia, arthralgia, and vomiting) that did not lead to discontinuation of the treatment, whereas side effects were major in Group A in a total of 49 patients (45.7%) of the type (asthenia, anorexia, sleep disorder, skin rash, vomiting, diarrhea, anemia, thrombocytopenia) were resolved after reduction of the treatment doses, and other more serious side effects requiring definitive discontinuation in 6 patients for poorly tolerated anemia, epileptic seizure, severe depression with suicide attempt, and dementia syndrome, the difference between the two groups was highly significant with ($p < 0.0001$).

4. Discussion

Hepatitis C is a major public health problem worldwide. In Morocco, due to the lack of recent epidemiological studies concerning the general Moroccan population, we only have the WHO data that estimates that HCV seroprevalence varies from 1% to 2%. While a study conducted in 2008 by A. Benouda reported that the prevalence of anti-HCV antibodies varies from 0.9% to 1.2% in the general population with an average age of positive cases of 50.4 y/o [2] versus 55 y/o in our study [33 - 82]. The HCV presents a great genetic heterogeneity; it can be classified into 8 major genotypes, themselves subdivided into more than 70 subtypes; their distribution varies according to the regions of the world, genotype 1 being the most frequently encountered in our regions, followed by genotypes 2 [3]. In our study genotype 1 was dominant with a frequency of 71.6%, followed by genotype 2 in 45 patients (27.2%). With the simplified routes, genotyping is not always necessary but remains of interest given its influence on the response to treatments, especially in cirrhotics and more essentially in genotype 3, whose sustained viral response is 5% less compared to other genotypes as reported in the study of Rafael Esteban. In our study, we did not observe the effect of genotype on the response to treatments, probably since genotype 3 does not exist in our series.

Among patients with chronic hepatitis C, 15% to 20% will be asymptomatic with normal transaminase levels and minimal histological lesions while 60% will have a disturbance of the liver balance associated with significant inflammation

and progressive fibrosis observed at liver biopsy; 20% of the latter will suffer from cirrhosis twenty years later [4] while in our study 88 patients (54.3%) were already cirrhotic, of which 61 were compensated and 27 were decompensated.

Pre-therapeutic evaluation of liver disease is essential because it conditions the patient's prognosis and modifies his management. The initial work-up must look for all other causes of chronic liver disease (alcohol, metabolic syndrome, HBV, hemochromatosis, autoimmune hepatitis, chronic cholestatic diseases, etc.). 6 patients had heart disease or 3.7%; obesity was observed in 5 patients or 3.08% with a metabolic syndrome in 3 patients or 1.85%; renal insufficiency in 19 cases or 12%; with 1 case of HBV-HCV association and another of HBV-HIV association; we also note that 14 patients or 8.6% were chronic alcoholics. Biologically, 19 patients (12%) had chronic kidney failure, 11 of whom were already undergoing hemodialysis, which is in line with the data in the literature. HCV infection is frequent in patients with renal failure, mainly hemodialysis patients, with a prevalence varying between 10% and 65% depending on the geographical area [5]; anemia was also noted before treatment in 20 cirrhotic patients with portal hypertension (12.34%); thrombocytopenia was present in 72 cirrhotic patients (44.44%). The treatment of HCV was initially limited to interferon alpha monotherapy but less than 20% of patients established a durable virological response; until 2002 when it was based on the combination of two molecules: Pegylated interferon alpha and Ribavirin; which made it possible to considerably increase the sustained virological response (SVR) but which did not exceed 40% to 50% [5]. In our study 107 (66%) patients initially treated with the former HCV treatments (Pegylated dual therapy or triple therapy). Pegylated interferon is administered subcutaneously once a week at a fixed dose for α-2a (180 µg/week) or adapted to the weight for α-2b (1.5 µg/kg/week). Ribavirin is administered per os at a weight-adjusted dosage (1000 mg/d if <75 kg or 1200 mg/d if >75 kg). This combination is prescribed for duration of 24 to 48 weeks depending on the viral genotype and the virological response observed under treatment. The results were unsatisfactory; SVR was obtained in 59 cases (55.14%); treatment failure was noted in 14 (13.1%) and relapse was observed in 14 cases which is in line with literature. The French survey done in 2010 [6] revealed the following results: 34.5% patients were virological non-responders, 19% responder-relapsers, and only 46.5% had sustained virological response as well as the EPIC 2010 survey [7]. A retrospective multicentric study performed in 28 French internal medicine, hepato-gastroenterology and infectious diseases departments reported the results of antiviral treatment in real life: 41.3% patients were virological non-responders, 28.1% responder-relapsers, and only 30.7% in sustained virological response. In Algeria [8] [9] a retrospective study on patient records (85) followed in consultation from January 2007 to September 2013 reported the following results: a sustained virological response (52.38%) Six non-responder patients (9.7%), 5 relapsers (8.6%), 3 premature cessation of treatment, 6 deaths, 6 lost to follow-up. There were important side effects, altering the quality of life of the patients; the premature definitive stop of the treatment was noted in 6 (5.

60%) patients for poorly tolerated anemia, epileptic seizure, severe depression with suicide attempt, and dementia syndrome; and other 43 patients (40.48%) had presented less serious side effects such as asthenia in 37 (34.57%), anorexia in 17 (15.88%), sleep disorder in 10 (9.34%), skin rash 6 (5.60%), vomiting 23 (21.5 %), diarrhea 18 (17%), tolerated anemia in 40 (37.38 %), thrombocytopenia 6 (5.60%) judged after reduction of the doses of the treatments. Our results are close to those of the literature [10] where the side effects observed under bitherapy PEG IFN + Ribavirin were Headache 47% - 62%; Fever 40% - 46%; Myalgia 37% - 56%; Arthralgia 24% - 34%; Nausea 35% - 43%; Anorexia 21%; Diarrhea 22%; Alopecia 21% - 36%; Rash/skin rash 20% - 24%; Asthenia 48% - 64%; Sleep disturbance 33% - 40%; Irritability 24% - 35%; Depression 22% - 31%. Dose reduction or discontinuation of treatment due to adverse effects was noted in our series, respectively, in 40.48% and 5.60% of cases compared to 42% and 14% in the international literature [11] [12].

New, highly effective and well-tolerated molecules belonging to the direct antivirals were marketed around 2014. These treatments make it possible to treat without interferon, which is responsible for many side effects. The cure rate in less than six months of well-followed treatment, whatever the HCV genotypes, is higher than 90% [13]. In Morocco DAA was marketed in 2016, and since the time of their introduction 55 patients (34% of our series) treated with DAA within the University Hospital of Hassan II. The most frequently proposed regimens were sofosbuvir SOF/Daclatasvir (DAC) ± RBV in 47 patients (85%). The duration of treatment was 12 weeks in 40 patients and 24 weeks in the remaining 15 patients. A sustained virological response at 12 weeks after the end of treatment was noted in 54 patients (98.18%), with failure in only one cirrhotic patient pre-treated with pegylated dual therapy. This is in line with the data in the literature, according to the results of the ANRS CO 22 HEPATHER cohort of 9895 patients recruited in 32 centers in France. DAA enabled the virus to be eliminated in almost all treated patients (95% in general) [14]. As well as 19 studies by Hugo Perazzo's team [15] involving a total of 57,433 people in eight territories or regions; the combined total proportion of patients with a sustained virological response was 98% (95% confidence interval, CI: 97 - 99; 18 studies; I2 = 94.1%) in per-protocol analyses and 96% (95% CI: 93 - 98; 8 studies; I2 = 68.1%) in intention-to-treat analyses [15]. In our study, the tolerance of DAA was excellent in all cases, with only five patients (9%) reporting adverse events that were minor and did not lead to discontinuation of treatment. There was only one discontinuation of DAAs due to hepatic encephalopathy with ascites fluid infection in a decompensated cirrhotic patient. The main adverse events were asthenia (n = 2) and joint pain or myalgia (n = 2) and vomiting in only one case, which is in line with the data in the literature, such as that of Marbet and al [16], where tolerance was excellent without recourse to discontinuation of treatment in any case [16].

Regardless of the prescribed therapeutic regimens, sustained viral response was observed in 64.77% in the cirrhotic group versus 66.2% in the non-cirrhotic

Table 2. Comparing the evolution of Child in cirrhotics before and after treatment.

	Before Treatment		After Treatment
Child A	**81**	**A5 (N = 61)** **A6 (N = 20)**	**A5 (N = 85)**
Child B		**4**	**0**
Child C		**3**	**3**

group (p = 0.565), treatment failure was noted in 12.5% in the cirrhotic group versus 5.4% in the non-cirrhotic group (p = 0. 091), and relapse was observed in 9% of the cirrhotic group versus 8% in the non-cirrhotic group (p = 0.509). This is what reported in the Astral-1 study which showed that the sustained viral response was almost the same between cirrhotics and non-cirrhotics with an SVR rate reaching 99% under Sofo + Velpa in the different cirrhotic or non-cirrhotic, naïve or treatment failure groups. Among the cirrhotic patients treated for HCV, 64 (73%) kept the same Child, with improvement in the Child of 21 (24%) patients with an average of 2 Points. This is consistent with the study by Jeblli S who showed that 34 out of 142 (23.9%) were delisted (while they were a candidate for liver transplantation) due to clinical improvement as well as the Lens S study which demonstrated an improvement in portal hypertension, and study by CFCarrillo which confirmed improvement in Child and Meld in cirrhotic patients treated for HCV (Table 2).

16 cirrhotic patients developed HCC in our series, 5 of whom were not yet treated for their HCV; 8 patients treated with pegylated dual therapy with an average delay of 4 years (1 and 10 years); 2 patients treated with pegylated dual therapy with treatment failure and only 1 patient treated with Sofo + Dacla in the first month of treatment. The mortality rate in our series was estimated at N = 14 (8.6%) of which 12 were treated with pegylated dual therapy and 2 with DAA (p < 0.0001). Our results are in line with the literature; according to the French study made on 9895 patients, followed for a median of 33 months, the statistical analysis allowed to highlight, among the 7344 patients who received DAAs before the end of the study, that this treatment was associated with a decrease in mortality and the occurrence of hepatocellular carcinoma. Indeed, after adjustment for various individual factors (age, stage of the disease, presence of other pathologies), patients treated with DAAs had a 52% lower risk of mortality and a 33% lower risk of developing liver cancer than patients with a similar stage of the disease but not taking DAAs [14].

5. Conclusion

Since the discovery of the hepatitis C virus, different molecules, interfering with certain stages of the viral cycle, have been developed to slow down the development of the disease. The therapeutic efficacy of recent treatments, essentially direct antiviral drugs, is such that it allows us to hope for a future eradication of

the virus. Our study also showed the superiority of DAA in terms of efficacy and tolerance compared to the old treatments of HCV, as well as the reduction of hepatic complications. However, it should be noted that having an effective treatment is not enough to eradicate the virus by 2030 as the WHO envisages, the road ahead is still long. It is necessary to encourage screening, which is a good way to fight against hepatitis C, because many people are carriers of HCV without being aware of it.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abreviations

DAA: Direct Acting Antivirals
DAC: Daclatasvir
HBV: Hepatitis B Virus
HCC: Hepatocellular Carcinoma
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
LDV: Ledipasvir
PEG-IFN: Pegylated Interferon
RBV: Ribavirin
SOF: Sofosbuvir
SVR: Sustained Viral Response
WHO: World Health Organization