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Unraveling the Impact of Direct-Acting Antivirals on Hepatitis-Linked Cirrhosis: A Comprehensive Analysis of Fibrosis, Child Score, and Disease Progression

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Abstract

The treatment of hepatitis C has undergone a significant boom since the advent of direct acting antivirals (DAA). Indeed, the interferon-ribavirin combination that has been used to treat hepatitis C has a virological response in only 45% of cases with significant side effects. The advent of direct-acting antivirals has changed the prognosis of cirrhotic patients with hepatitis C. DAAs have ensured a sustained viral response in the majority of patients. Our work aims to see the evolution of hepatitis C patients at the cirrhosis stage under DAA. We conducted a retrospective study over 15 years (January 2009, January 2024) including all patients with post-viral cirrhosis C, whom we divided into two groups: group A, cirrhotic patients who received ribavirin and interferon, and group B, patients on DAA. From January 2009 to January 2024, we conducted a study of 182 patients with viral hepatitis C, including 102 cirrhotic patients. The mean age was 55 years. 66% of patients were initially treated with the ribavirin interferon combination, while 34% received direct-acting antivirals (DAAs). Since the introduction of DAAs, the most commonly used regimens have been sofosbuvir/daclatasvir with or without ribavirin and sofosbuvir/ledipasvir with or without ribavirin. Group A achieved sustained virological response (SVR) in 60% of cases, with notable side effects. In Group B, SVR was 98.18%, with improved tolerability and fewer side effects than previous treatments. Fifteen patients developed hepatocellular carcinoma (HCC), with a significantly lower mortality rate in those treated with DAAs compared with pegylated dual therapy (p: 0.001).

Keywords

Post-Viral Cirrhosis C, Pegylated Interferon, Direct Acting Antivirals, Sustained Viral Response, Child Score, Fibrosis

1. Introduction

Treatment of hepatitis C has long relied on the ribavirin/interferon/pegyl combination, with only 45% of patients achieving a sustained viral response; this rate is lower in patients with cirrhosis [1]. Direct Acting Antivirals (DAA) have improved sustained viral response, prevented cirrhosis-related complications in compensated patients, and enhanced the CHILD score in patients with advanced Child scores [1]. In cirrhotic patients, the advantage of antivirals lies in their tolerability and efficacy compared with conventional treatments, enabling, in some cases, regression of fibrosis [2].

2. Aim

Our work mainly aims to compare the therapeutic response of patients with post-viral cirrhosis C on DAA with those on ribavirin or pegylated interferon and overall survival in patients with the two treatment regimens.

3. Patients and Methods

3.1. Type and Period of Study

We conducted a retrospective monocentric comparative and analytical study over 15 years (January 2009, January 2024), including all cirrhotic patients followed at the Hassan II University Hospital in Fez. Group A comprises patients with post-viral cirrhosis C treated with DAA, and group B includes patients with post-viral cirrhosis C treated with ribavirin and interferon or combination of both treatments. The mean follow-up period was 36 ± 12 months.

3.2. Patients' Selection Criteria

- Patients over 18 years of age;
- Patients with viral hepatitis C treated in our training program (hospitalization, consultation, or day hospital);
- Patients on pegylated interferon, ribavirin, or direct-acting antivirals;
- Consent for the study;
- Complete medical records.

3.3. Patients'Exclusion Criteria

- Patients not consenting to the study;
- Non-cirrhotic patients;
- Patients with incomplete medical records.

3.4. Data Collection

We collected epidemiological, clinical, paraclinical, and therapeutic data from patients meeting the inclusion criteria using the patients' computer files after approval by the local ethics committee. These data included patients' symptoms, medication use, consumption of alcohol or other hepatotoxic foods, disease presentation, and the results of biological and radiological tests carried out. Liver function was assessed by clinical criteria (presence of ascites, digestive bleeding, hepatic encephalopathy) and biochemical criteria (platelet count, PT, INR, transaminases, bilirubin, albumin). The CHILD and MELD scores were calculated for the patients, and the clinical-biological evolution of the 2 case and control groups was recorded. Statistical analysis was performed using SPSS V22 software, with a value of $p < 0.05$ considered statistically significant.

3.5. Comparative Study

To determine the effect of DAA on patients with post-viral cirrhosis C, we divided patients into groups A (treated with ribavirin) and B (treated with DAAs). We compared sustained viral response in the two groups, CHILD before and after antiviral treatment, and mortality in the two groups.

3.6. Statistical Analysis

The data collected were entered in Excel.

Statistical analysis was performed using SPSS v22 software. Quantitative values were reported as mean, median, and standard deviation. We used the χ^2 or Fisher's statistical test with a significance level of 0.05 for qualitative values. The Pearson test is used to express correlations.

3.7. Definitions

- **CHILD Score:** It evaluates the severity of liver disease, the factors are: bilirubin, albumin, prothrombin time, and encephalopathy. There are three classes: A, B, and C, with C being the most severe.
- ***MELD Score*:** Model for end stage liver disease, is a numerical scale to assess the verity of liver disease, based on creatinine, bilirubin and INR. The score ranges from 6 to 40, with higher scores indicating a greater need for a liver transplant.

4. Results

Between January 2009 and January 2024, we enrolled 105 cirrhotic patients.

4.1. Group A: Patients on Interferon and Ribavirin

- ***Patient demographics*:** Group A were patients on interferon and ribavirin (n = 60). They had a mean age of 65 years (36 to 88 years) with a clear male predominance, sex ratio M/F: 0.62. The most common comorbidities were diabetes (10%), hypertension (29%), metabolic syndrome (2%), renal disease

was found in 6% of patients. Excessive alcohol consumption was found in 8% of patients and smoking in 20% of patients. There was one case of HBV-HVC co-infection.

- ***Clinical signs*** were dominated by asthenia and arthralgia. At diagnosis: Most patients had CHILD A (n = 50, 84%), B7 (n = 6, 10%), and CHILD C12 in 4 patients. The mean MELD was 12 (84% had a mean MELD of 7, 10% a MELD of 12, and 6% a MELD of 17). Renal failure marked by high creatinine clearance was found in 3 patients, all at the hemodialysis stage. At the time of diagnosis, ten patients had hepatocellular carcinoma (HCC), with two patients requiring therapeutic abstention due to the metastatic nature of the HCC
- ***Before treatment***: 10 patients had decompensated cirrhosis at diagnosis, including 6 with ascitic decompensation, 7 with hemorrhagic decompensation, and 2 with hepatic encephalopathy. In group A, the most frequent genotype was 1b in 35 patients (68%), 2a in 11 patients (21%), 3A in one patient, and undetermined in the remainder. The mean viral load was 4.5 ± 1.5 log. Cryoglobulin was positive in one patient, and renal involvement in 3 patients marked by elevated creatinine clearance, all of whom are on hemodialysis. The fibroscan showed a mean elastometry of 17.3 ± 9.24. The mean fibrotest was 7 ± 2. A liver biopsy was performed in 4 patients when there was doubt about the presence of cirrhosis and showed F4 fibrosis in all.
- ***Post-treatment***: All patients in group A were treated with pegylated interferon and ribavirin for 12 ± 3 months.
- ***Outcomes***:
  - **Sustained viral response:** was observed in 60% of patients (n = 36).

Side effects: The main side effects were headache 47% - 62%, fever 40% - 46%, myalgia 37% - 56%, arthralgia 24% - 34%, nausea 35% - 43%, anorexia 21%, diarrhea 22%, alopecia 21% - 36%, rash 20% - 24%, asthenia 48% - 64%, sleep disorders 33% - 40%, irritability 24% - 35% and depression 22% - 31%. Dose reduction or treatment discontinuation due to adverse effects were noted in our series, respectively, in 40.48% and 5.60% of cases.

- **HCC and mortality:** Six patients had HCC at diagnosis and 4 patients developed HCC at follow-up, 2 of whom required therapeutic abstention (multifocal HCC). For the remaining patients, four were treated with systemic therapy (sorafenib), 2 with radiofrequency, one with alcoholism, and one with surgery. All treated patients were put on pegylated interferon and ribavirin, with progression of HCC in 5 patients and a favorable outcome in 3. The mortality rate was 16% (n = 10, five patients following decompensation of post-viral cirrhosis C and five patients following HCC).
- **Liver function improvement:** Among cirrhotic patients treated with the ribavirin-pegylated interferon combination, 70% of patients retained the same Child, with worsening of the Child in 14% of patients and improvement of the Child in 16% of patients, with a mean of 2 points.

4.2. Group B: Patients on Direct Acting Antivirals

- ***Patient demographics***: Group B were patients on DAA (n = 45). They had a mean age of 64 years (38 to 85 years). The sex-ratio M/F: 0.7. The most common comorbidities were diabetes (10%), hypertension (29%), metabolic syndrome (2%), and renal failure was found in 11% of patients. There was one case of HBV-HIV co-infection. No patient had excessive alcohol consumption. The most frequent symptoms were asthenia, joint pain, and ascitic decompensation (n = 2). Biology showed cytolysis in two patients.
- ***Before treatment***: At the time of diagnosis, cirrhosis was compensated in most patients (n = 30, 66%) and decompensated in the remainder. The main decompensations were ascitic (n = 9), hemorrhagic (n = 6), and hepatic encephalopathy (n = 5). HCC was noted at the time of diagnosis in 5 patients (11%). Most patients had CHILD A (n = 30, 66%), CHILD B (n = 11, 24%), and CHILD C (n = 4, 10%). The mean MELD was 13 (70% had a mean MELD of 8, 13% a MELD of 12, and 17% a MELD of 18). The most frequent genotype is genotype 1b (n = 25, *i.e.*, 55%), followed by genotype 2A (n = 12, 26%), genotype 1A (n = 6, *i.e.*, 13), genotype 1a and four co-infection (n = 1) and genotype 1b and 1A co-infection (n = 1). The mean viral load was 5 ± 2 log. Creatinine clearance was elevated in 5 patients (11%). Systematic fibroscan and fibrotest showed advanced fibrosis.
- ***After treatment***

The most common treatment regimens were sofosbuvir SOF/Daclatasvir (DAC) ± RBV in 85% of patients and (SOF)/ledipasvir (LDV) in the remaining patients.

Sofosbuvir/Daclatasvir 400/60mg was administered once daily for 12 weeks in 75% of patients and for 24 weeks in 25% of patients. It was associated with ribavirin in 10% of cases for 12 weeks. Ribavirin dosage was between 800 - 1400 mg depending on patients weight. Sofosbuvir ledipasvir 400/90mg was administered once daily in 15% of patients for 12 weeks.

- ***Outcomes***:
  - **Sustained viral response:** was achieved in 98.18% of patients treated with DAA and 100% treated with sofosbuvir + daclatasvir ribavirin.
  - **Tolerance and adverse events:** Tolerance to DAAs was excellent in all cases, with only five patients (9%) reporting minor adverse events that did not lead to treatment discontinuation. The only discontinuation of DAAs due to hepatic encephalopathy with ascites fluid infection was in a decompensated cirrhotic patient. The main adverse events were asthenia (n = 2), joint pain or myalgia (n = 2), and vomiting in only one case.
  - **HCC and mortality:** Five patients had HCC at diagnosis. Two patients were on systemic therapy (Sorafenib), and three patients were on chemoembolization. One patient developed HCC at seven weeks of treatment and underwent surgery with a good outcome.
  - **Liver function improvement:** Among cirrhotic patients treated with di-

rect-acting antivirals, 63% retained the same Child, with worsening of the Child in 9% of patients and improvement of the Child in 28%, with a mean of 2Pt.

- **Mortality:** The evolution in this population was marked by death in one patient, while a favorable response was noted in the remaining patients, all of whom are currently under surveillance.

4.3. Statistical Analysis

The statistical test used was the Chi-2 test. The items analyzed were sustained viral response, Child, CHC, and mortality on direct-acting antivirals.

Direct-acting antivirals were associated with a sustained viral response (p: 0.042) and improved CHILD score (p: 0.003). Factors not influencing therapeutic response were CHILD A (p: 0.09) and the absence of HCC at diagnosis (p: 0.078).

In terms of mortality, the direct-acting antiviral group showed significantly lower mortality than the pegylated interferon group (p: 0.01), particularly in the HCC group ($p < 0.001$). Table 1 summarizes the main results:

5. Discussion

The hepatitis C virus is genetically highly heterogeneous and can be classified into eight significant genotypes, which are themselves subdivided into more than 70 subtypes. Their distribution varies worldwide, with genotype one being the most frequently encountered in our regions, followed by genotype 2 [3]. Among patients with chronic hepatitis C, 15% to 20% will have advanced disease, normal

Table 1. Main results of interferon and ribavirin versus DAA.

	Group A: interferon + Ribavirin, n = 60	Group B: DAA, n = 45	Statistical analysis
Age	65 y/o (36 - 88 y/o)	64 y/o (38 - 85 y/o)	p: 0.09
Sex-ratio: M/F	0.62	0.7	p: 0.097
Comorbidities	Arterial hypertension 29% Diabetes 10% Kidney failure 6%	Arterial hypertension (14%) Kidney failure (11%) Excessive Alcohol consumption (0%)	p: 0.086
CHILD after treatment	A: 69% B: 15% C: 10%	A: 80% B: 14% C: 6%	p: 0.003
Decompensation	Ascitis (n = 6) Bleeding (n = 7) Hepatic encephalopathy (n = 2)	Ascitis (n = 9) Bleeding (n = 6) Hepatic encephalopathy (n = 5)	p: 0.09
HCC	16%	11%	p: 0.078
SVR	60%	98.18%	p: 0.042
Mortality rate	16%	6%	p: 0.01
Survival rate HCC	20%	90 %	$P < 0.001$

transaminase levels, and minimal histological lesions. In comparison, 60% will have a disturbance of the liver balance associated with significant inflammation and progressive fibrosis observed on liver biopsy, and 20% of the latter will suffer cirrhosis twenty years later [4].

Pre-therapeutic assessment of liver disease is essential, as it conditions the patient's prognosis and modifies his or her management. The initial work-up should investigate all other causes of chronic liver disease (alcohol, metabolic syndrome, HBV, hemochromatosis, autoimmune hepatitis, chronic cholestatic diseases, etc.). In our series, the comorbidities found in our patients were diabetes in 9 patients, heart disease in 6 patients, obesity in 5 patients (3.08%), metabolic syndrome in 3 patients (1.85%), renal insufficiency in 12%, with 1 case of HBV-HCV association and another of HBV-HIV association. 8.6% were chronic alcoholics.

Biologically, 12% had kidney failure, 11 of whom were already on hemodialysis, which is in line with the literature or 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 in 12.34% of cirrhotic patients, and thrombocytopenia was present in 44.44%.

Treatment of hepatitis C-linked cirrhosis was initially limited to interferon-alpha monotherapy, but less than 20% of patients achieved a sustained virological response. Until 2002, it was based on combining two molecules: Pegylated interferon-alpha and Ribavirin, which considerably increased the sustained virological response, although this did not exceed 40% to 50% [5]. In our study, 60 patients were initially treated with previous hepatitis C therapies (pegylated therapy). Pegylated interferon is administered subcutaneously once a week at a fixed dose for α-2a (180 µg/week) or adapted to weight for α-2b (1.5 µg/kg/week). Ribavirin is administered per os at a weight-adjusted dose (1000 mg/d if < 75 kg or 1200 mg/d if > 75 kg). This combination is prescribed for 24 to 48 weeks, depending on viral genotype and virological response to treatment. The results were unsatisfactory: SVR was achieved 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 the data in the literature, such as the French survey carried out in 2010 [6], which revealed the following results: 34.5% of patients were virological non-responders, 19% responder-relapsers, and only 46.5% sustained virological response, as well as the EPIC 2010 survey [7].

A retrospective multicenter study carried out in 28 French departments of internal medicine, hepato-gastroenterology, and infectious diseases reported the results of antiviral treatment in real life: 41.3% patients were virologically non-responders, 28.1% responder-rejecters, and only 30.7% sustained virological response [8].

On the other hand, significant side effects were observed, altering patients' quality of life. Our results are similar to those reported in the literature, where

the side effects observed with pegylated interferon and ribavirin therapy were headache 47% - 62%, fever 40% - 46%, myalgia 37-56%, arthralgia 24% - 34%, nausea 35% - 43%, anorexia 21%, diarrhea 22%, alopecia 21% - 36%, rash 20% - 24%, asthenia 48% - 64%, sleep disturbance 33% - 40%, irritability 24% - 35% and depression 22% - 31%. Dose reduction or discontinuation of treatment for adverse effects was noted in our series, respectively, in 40.48% and 5.60% of cases, compared with 42% and 14% in the international literature [9] [10].

New, highly effective, well-tolerated molecules from the DAA class came to market in 2014. These treatments do away with the need for interferon, responsible for numerous side effects. The cure rate in less than six months of well-monitored therapy, regardless of HCV genotype, is over 90% [11]. The most frequently proposed regimens were sofosbuvir SOF/Daclatasvir (DAC) ± RBV in 85.45% of patients, followed by (SOF)/ledipasvir (LDV)±ribavirin (RBV). The treatment duration was 12 weeks in most cases. A sustained virological response at 12 weeks after the end of treatment was noted in 98.18% of patients with failure in a single cirrhotic patient pre-treated with pegylated dual therapy. Our data concur with those of the ANRS CO 22 HEPATHER cohort of 9895 patients recruited from 32 centers in France, where DAAs were able to eliminate the virus in almost all treated patients (95% overall) [12]. A meta-analysis of 19 studies by Prazzol et al. involving a total of 57,433 people concluded that SVR was 98%, which is in line with the results of our study [13].

In our study, tolerance to DAAs was excellent in all cases, with only 9% of patients reporting minor adverse events that did not lead to treatment discontinuation. The only discontinuation of DAAs due to hepatic encephalopathy with ascites fluid infection was in a decompensated cirrhotic patient. The main adverse events were asthenia (n = 2), joint pain or myalgia (n = 2), and vomiting in only one case, which is in line with data in the literature, such as that of Marbet et al. where tolerance was excellent, with no need to discontinue treatment in any case [14]. In addition, the mortality rate was significantly lower in HCC patients on DAAs ($p < 0.001$).

Thus, our results concur with those of a French study including 9895 patients over an average duration of 33 months with 7344 patients on DAA. This treatment was associated with a lower rate of mortality and HCC. Indeed, after adjusting for individual factors (age, stage of 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 disease but not taking DAAs [14].

6. Conclusion

Since the discovery of the hepatitis C virus, various molecules interfering with specific stages of the viral cycle have been developed to slow the development of the disease. The therapeutic efficacy of recent treatments, essentially DAA, is to raise hopes of eradicating the virus soon. Our study also demonstrated the supe-

riority of DAAs in terms of efficacy and tolerability compared with older treatments for CVH and a reduction in hepatic complications. However, it should be noted that effective treatment is not enough to eradicate the virus by 2030, as the WHO envisages; there is still a long way to go. We need to encourage screening, which is a good way of combating hepatitis C.

Conflicts of Interest

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

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Abréviations

DAA: Direct-acting antivirals

DAC: Daclatasvir

HCC: Hepatocellular carcinoma

LDV: Lédipasvir

RBV: Ribavirine

SVR: Sustained viral response

VHC: Viral hepatitis C

VHB: Viral hepatitis B