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Viral Load during the First Month of Direct-Acting Antivirals or Interferon Plus Ribavirin for Hepatitis C Infection

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Abstract

Background/Aims: A rapid decrease in liver inflammation following hepatitis C resolution can account for hepatocellular carcinoma recurrence. The aim of this study is to provide further evidence to support this theory.

Methods: Viral load and liver function at days 0, 7, 14 and 28 of therapy in 79 patients with hepatitis C treated with direct-acting antivirals, and at days 0 and 28 in 19 patients treated with interferon and ribavirin.

Results: Baseline viral load was 6.2 log in patients treated with direct-acting antivirals and 6.3 log in patients treated with interferon and ribavirin (p= 0,502); on day 28 these values were 0.2 log versus 2.3 log (p<0,001). At baseline, AST was 82.1 IU in the Direct-Acting Antivirals group vs. 55.9 IU in the interferon and ribavirin group (p<0.016). After 28 days, AST fell to 30.0 IU in the former group, below the 51.1 IU values observed in the latter (p<0.002). AST decreased in 76 (96%) patients in the Direct-Acting Antivirals group but only in 11 (58%) in the interferon and ribavirin group (p<0.05). Viral load decreased 4 log on day 28 in the interferon and ribavirin group; this result had been reached on day 7 in the Direct-Acting Antiviral group.

Conclusion: Direct-acting antivirals induce a major decrease in viral load and inflammation than interferon and ribavirin by the end of the first week of therapy. This effect may have some influence on the immunologic surveillance of inflammatory cells and promote neoplastic recurrence.

Keywords: Direct-acting antivirals; Hepatitis C virus; Hepatocellular carcinoma; Interferon

Abbreviations

HCC: Hepatocellular Carcinoma; DAA: Direct-Acting Antivirals; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PEG+ RBV: Pegylated interferon+Ribavirin; TE: Transient Elastography

Introduction

Recent retrospective studies have found an unexpectedly high probability of hepatocellular carcinoma (HCC) recurrence in patients treated with Direct-Acting Antivirals (DAA); *de novo* HCC and even extra hepatic malignancies can also be more frequent in this setting [1-4]. The exact biological and biochemical pathways that result in HCC in patients with cirrhosis have not been fully understood to date, but Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) seem to play an oncogenic role. Once the tumour has been diagnosed, few patients can undergo a curative treatment either because the patient is too old, the tumour is too big or the liver function is too poor. Even in the cases where a curative treatment is performed, recurrence remains very high [5]. A recently formulated hypothesis for the even higher probability of recurrence in patients treated with DAA suggests that after a massive eradication of HCV in a short period of time, there is a rapid disappearance of immune cells and mediators that accumulate in the liver to control the infection. This situation would disrupt the immunological surveillance over the so far few remaining tumour cells, giving rise to a multifocal and often fatal HCC [6]. The present study aims to add further evidence of the rapid, intense decline in viral load in patients treated with DAA compared with pegylated interferon plus ribavirin (PEG+RBV), thus supporting the disruption of immunological surveillance as a hypothesis for HCC recurrence.

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Patients and Methods

Patients treated with PEG+RBV

We reviewed 100 patients treated for HCV before the advent of the first DAA (2013). Indications for treatment were those presently accepted in clinical guidelines, in brief: any degree of liver fibrosis in the absence of decompensated cirrhosis, severe anaemia, leukopaenia or thrombocytopenia, uncontrolled thyroid or psychiatric disease, any immune disease or severe comorbidity. In all cases, fibrosis was estimated with the FIB4 score or Transient Elastography (Fibroscan Echosens 402) (TE) if available, HCC was ruled out by ultrasonography, and standard liver function tests, viral load and genotype were determined before starting and after 28 days of treatment. From these 100 patients, we selected those 19 who had been compliant with medication, had completed at least one month of therapy and had shown response to therapy as estimated by at least a 2 log decrease in viral load after 28 days of therapy. In these patients, viral load and standard liver function tests were determined on days 0 and 28 of treatment.

Patients treated with DAA

This study also includes the first 79 patients treated with DAA in our hospital in 2015. Indications for treatment were advanced (F2 to F4) fibrosis, human immunodeficiency virus coinfection, renal failure or extra hepatic manifestations of HCV infection irrespective of the degree of fibrosis. TE was available in all cases. As in the PEG+RBV group, blood samples were obtained on days 0 and 28 of treatment. In order to monitor liver function and viral load in these first patients, additional blood samples were obtained on days 7 and 14 of treatment. All DAA regimens included sofosbuvir in combination with simeprevir in 54 patients (68%), ledipasvir in 18 cases (24%) and daclatasvir in 6 (8%). Ribavirin was added when necessary according to clinical guidelines. In 1 patient (1%) sofosbuvir was combined only with ribavirin.

Table 1 compares the clinical and analytical data of the 79 patients treated with DAA and the 19 patients treated with PEG+RBV at baseline and on the first 28 days of therapy.

Sample Size

To ensure a statistical power of 80% in order to detect differences in the contrast of the null hypothesis through a two-tailed chi-square test for two independent samples with a level of significance of 0.05, and assuming that the proportion of patients with a decrease in serum transaminases in the DAA group is 90% and the proportion in the PEG+RBV group is 60% in an 8:2 ratio, 68 patients had to be included in the DAA group and 17 in the PEG+IFN group.

Statistical analysis

Quantitative variables are shown as mean and 95% confidence interval and categorical variables as absolute and relative frequencies. For the bivariate analysis the Student t-test was used for continuous variables with normal distribution or the Mann-Whitney non-parametric test otherwise. The chi-square test and Fisher's exact test were used for categorical variables. The level of statistical significance was two-sided 5% ($p < 0.05$). The SPSS v.22 (IBM Corporation, Armonk, New York) was used for statistical analysis.

Ethical considerations

Approval from an independent Ethics Committee for Clinical research (Ethics Comittee "Fundació Unió Catalana d'Hospitals") was obtained. This study was conducted in accordance with the principles of the Declaration of Helsinki. All data were recorded in an anonymous database. Informed consent was obtained from all patients.

Results

Our study shows that at baseline, patients in the PEG+RBV group were younger, had less advanced fibrosis and less inflammation of the liver as estimated by AST than patients in the DAA group. By contrast, both groups were similar with respect to genotype distribution, serum bilirubin and serum albumin. There was a higher proportion of males in the PEG+RBV group than in the DAA group. After the first month of treatment, AST levels had decreased to less than half of the initial values in the DAA group while they remained unchanged in the PEG+RBV group. Viral load plummeted after the first week of treatment in the DAA group to a level that had hardly been reached by patients treated with PEG+RBV after 4 weeks of therapy, an observation which is especially relevant when clinical conditions such as older age and more advanced fibrosis were considered to be adverse predictors of response [7]. The sharp decrease in viral load observed after the first week of treatment in the DAA group sloped down softly until day 28. Other parameters that estimate liver function, such as serum bilirubin and serum albumin, remained similar in both groups at baseline and after 28 days of treatment, although there was a tendency to an increase in serum bilirubin in patients treated with DAA, probably related to the use of protease inhibitors. These results show that DAA cause an extremely rapid decrease of the inflammatory reaction to HCV infection in the liver, while interferon seems to act far more slowly. The decrease in viral load induced by DAA occurs as early as in the first seven days of therapy.

Discussion

The irruption of DAA in the therapeutic armamentarium against HCV infection has represented a revolution in terms of efficacy and tolerance to such an extent that a possible elimination of HCV may be achieved by 2030 [8]. Advanced countries have started treating infected patients at all stages of the disease, or selectively in patients at higher risk of liver complications [9,10]. DAA act at an intracellular level by blocking different proteins (NS5A, NS3A) or enzymes (RNA polymerase) that are essential for viral replication and their effect is consequently immediate. In contrast, interferon, the most widely used drug for hepatitis C until the DAA era, acts by modifying the immunological response to infection and requires the elimination of infected hepatocytes, producing a more delayed result [11]. Besides, healing rates with the association of ribavirin plus pegylated interferon hardly reach 50% of patients, but range between 90 and 100% with DAA [12]. HCV infection affects around 1.5% of the population worldwide and progresses to cirrhosis in 10-20% of cases after 20 years of infection [13]. Cirrhosis is directly related with the development of HCC, the fifth most common tumour in humans: estimates are that 20% of patients with cirrhosis develop this tumour after a 5-year follow-up period and, despite a considerable amount of research, it still carries a dismal prognosis [5]. Although screening programmes are strongly encouraged in clinical guidelines, they show conflicting results in terms of periodicity and efficacy [14,15]. Thus, every therapy addressed at eradicating the infection has been viewed as a promising step towards prevention; however interferon-based therapy, the best treatment available until 2014, was not appropriate for patients with advanced disease, was not well tolerated by others and had limited efficacy. It is in this setting that DAA, with high efficacy,

lack of remarkable side effects and few restrictions in patients with advanced disease, were received with enthusiastic expectations by both patients and hepatologists. Recent publications, however, have cast a shadow over these exciting therapeutic advances suggesting an unexpected high recurrence of previously cured HCC in patients treated with DAA [4,5]. Different hypotheses may explain this paradoxical effect. It is well known that HCC recurrence 5 years after a curative treatment is as high as 15% in liver transplantation, 18% in radiofrequency ablation and 70% in surgical resection, these values having been confirmed in prospective studies [16-18]. These results seem to show that either the treatment has not been as radical as it was expected, or that the diseased liver is especially prone to develop new HCC in some patients [19]. In the study of Reig et al. [1] tumour recurrence after a curative treatment was as high as 27.6% even after an observational period of 5.7 months between curative treatment and DAA administration. It could be argued that this period of time was too short and that there is no genomic profile of the recurrent lesions to distinguish from the novo HCC, but at any rate, these results are of concern if confirmed. Similar results were observed in the study by Alberti et al. [4]. However, other retrospective studies did not find an increased risk of HCC recurrence [20,21]. Confirmation of these findings in prospective studies is needed.

The possibility of a direct oncogenic effect of DAA cannot be ruled out but is unlikely since these drugs have been extensively investigated before marketing. Furthermore, DAA are a heterogeneous group of drugs that act on different substrates or at different steps of viral replication, such as on proteases or polymerases. This suggests that high tumour recurrence occurs much more as a result of their powerful effect on viral load than of the intrinsic metabolic pathways.

The study published by Reig et al. [6] hypothesizes that the unexpectedly high tumour recurrence rate observed in cirrhotic patients with previously cured HCC results from a very rapid decrease in viral load. This effect, which we confirm in our study, would cause a drastic reduction in the inflammatory response to the infection which in turn would affect the immunologic surveillance role of inflammation cells against neoplastic cells, either residual from an already treated or de novo tumour. Our study also confirms the rapid decrease of liver transaminases after DAA administration as a surrogate marker of hepatic inflammation. Neither the study by Reig et al. [6] nor our study directly measured inflammation mediators after treatment with DAA. The study by Owusu et al. [22] was specifically addressed at finding evidence of such an immunological response to antivirals. In this study, the correlation between CD4 and CD8 T cells in the inflammatory milieu was significantly affected after DAA treatment in that HCV- specific CD8+ T cells failed to recover upon DAA therapy. Further evidence of immunological disturbances during treatment with DAA is described by Villani et al. [23] found a 4-fold increase in VEGF during therapy and a decrease of IL-10 and TNF-Alpha coinciding with HCV clearance. These results add evidence to the hypothesis of the study by Reig et al. The rapid and aggressive recurrence of HCC would not have been observed with previous treatments available for HCV infection because of a steady decrease of inflammatory mediators [24]. Consistent with this hypothesis, our findings also confirm only a mild decrease in inflammation after four weeks of therapy with PEG+RBV. Although some studies have also pointed to the possibility that this latter therapy may also be responsible for HCC recurrence, evidence is scarce and, conversely, PEG+RBV has been used to prevent tumour relapse before or after the administration of a curative treatment [25].

Therapy for HBV infection seems an attractive model to compare with HCV: HBV is known to be a predictor of the development of cirrhosis and HCC, drugs generally used (tenofovir or entecavir) are well tolerated, can be administered in advanced liver disease and reduce viral load to undetectable in most instances [26]. However, they differ in that HBV cannot be completely eliminated from the liver (and therefore requires lifelong treatment), and in that viral load falls steadily from the initiation of therapy in HBV but sharply in HCV infection. Several lines of evidence suggest that decreasing viral load either before or after a curative therapy (resection, ablation) decreases the likelihood of tumour recurrence in HBV infection [27,28]. Again, the rapid viral clearance induced by DAA seems to play a role in the high tumour recurrence rate in HCV infection, an effect that has not been observed in most studies with HBV infection, where HBV DNA decay is only of 2.64 log after 12 weeks of therapy with tenofovir [29].

Results

The results observed in our study are limited by its retrospective nature: we could not match both groups of patients for fibrosis or age. However, the fact that decrease in viral load and inflammation was poorer in the PEG+IFN group than in the DAA group of patients, although they were younger and had less fibrosis, strengthens the impact of DAA in these parameters. It can also be argued that our observation reflects only a lesser efficacy of PEG+RBV as compared with DAA in terms of eradication of HCV infection and that the PEG+RBV group should include only patients finally cured. Although DAA are clearly superior to previous therapies, this is partly attributable to drop-offs during therapy due to a poor tolerance to PEG+RBV, an effect that has been solved in our study by selecting only patients who completed 28 days of treatment in both groups. Besides, most patients who fail to resolve HCV infection with PEG+RBV have negative viral loads during therapy, which indicates that this combination of drugs is also highly efficient in controlling viral replication, but other factors such as time of therapy, tolerability and side effects play a major role in eradication. A final limitation of the study is the lack of direct markers of inflammation such as interleukins and other cytokines. Availability of viral load and transaminases on days 7, 14 and 28 in all cases treated with PEG+IFN and in patients with treated for HBV would have also been interesting. If prospective results confirm such a high recurrence rate of hepatocellular carcinoma after DAA therapy as the cited studies suggest, and if this is due to a massive decrease in viral load and inflammation as our and other lines of evidence indicate, treatment will have to be prescribed after a cautious consideration of advantages in some subsets of patients. There may be a place for less potent drugs, or for a combination with modulators of immune response to preserve immunologic surveillance.

Conclusion

In conclusion, our study shows that transaminases decrease quickly in HCV-infected patients treated with DAA, which reflects a higher effect on inflammation than PEG+RBV. This finding supports the theory of a disruption of the immunologic surveillance role of inflammatory cells in the prevention of hepatocellular carcinoma recurrence. Most of the effect in the control of viral load occurs as early as during the first week of DAA therapy, while a similar result was not achieved with PEG+IFN after 28 days of treatment.

Key Points

- Our study shows that the intensity of viral load decrease

after 4 weeks of therapy in patients treated with PEG-interferon plus ribavirin is similar to that observed after only one week with Direct-acting antivirals.

- Similarly, Serum transaminases decrease much faster in patients treated with Direct-acting antivirals than with PEG-interferon plus Ribavirin.

- The rapid resolution of liver inflammation observed in our study after treatment with Direct-acting antivirals but not with PEG-interferon with ribavirin may contribute to a higher rate of hepatocellular recurrence described in other investigations.

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