TREATMENTS OF HEPATITIS C VIRUS LIVER CIRRHOSIS WITH PEGYLAT INTERFERON-RIBAVIRIN AND INTERFERON FREE – COMPARATIVE STUDY

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ABSTRACT

The article describes the adverse effects and efficiency of hepatitis C virus liver cirrhosis treatments available through the National Health Insurance Services, on a population of patients hospitalized at Victor Babes Infectious and Tropical Diseases Hospital, from 2012 to 2016. The population of patients was split into two distinct groups, for which we've recorded and comparatively analyzed demographic, clinical and paraclinical characteristics in a database. An evident success was recorded, from the point of view of hitting a clinical SVR index, in the DAA therapy group A, 87% percent compared to 2% in group B for the traditional standard therapy of PegInterferon + Ribavirin. Likewise, the number of adverse effects was lower in Group B versus Group A. Some side effects remained specific to the current cirrhosis treatment, which should be closely monitored.

Keywords: hepatitis C virus, direct action antiviral (DAA), sustained virological response (SVR)

INTRODUCTION

Hepatitis C virus infection is a disease with a serious health impact on the human organism. In periods ranging from a few years to decades, the patient could develop important complications due to the chronic evolution of the disease, complications like liver cirrhosis or hepatic adenocarcinoma (1). The evolution of the disease can be accelerated through drug abuse or coinfection with Hepatitis B Virus or HIV (2). It is a health issue of global scale, with more than 170 million registered infected humans.

Currently, there is no hepatitis C virus (HCV) vaccine, and the development of one in the near future is improbable due to the multitude of challenges related to this issue, the most important of which is the extreme diversity of the virus, which shows a divergence at amino acid level of 30% for all 7 major genotypes (3).

For any HCV treatment to be successful, it should both totally eliminate the virus (viral clearance), as well as improve the overall clinical health. One of the clinical standards most used for the confirmation of success in treatment is the *sustained virological response* (SVR) which shows the absence of the C virus ARN in blood samples after treatment completion. A positive SVR mark is closely correlated with an improved clinical tableau, as well as a drop in mortality rates.

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Short history of HCV treatment (Fig. 1)

After the discovery of the virus responsible for hepatitis C in 1989, independently by the Centre of Disease Control and CHIRON, the first treatment approved for use was interferon alfa-2B in 1991, a drug that interfered with the viral replication through a mechanism that involved the organism's own immune response. In 1998, the combination of interferon and ribavirin (ribonucleic analogue used as a nucleoside inhibitor) was approved, followed in 2001 by PEGylated interferon (Peg interferon). A period of intense research in the pharmaceutical industry followed, as well as in the academic medium, for the discovery of new molecules with a direct antiviral effect against the HCV, independent from the body's own immune response – and especially without the addition of the immunomodulatory interferon, a substance known to produce a multitude of adverse effects, generally at fault for the therapeutic failure of this variation of therapy.

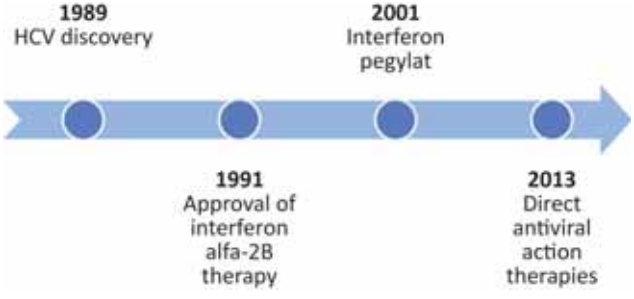

Figure 1. *Historical evolution of HCV treatment strategies*

During this evolution, the efficiency of the treatment represented by the SVR has varied from 30% in the case of interferon alfa-2B, 65% in the case of the interferon + ribavirin combination, to almost 75% for PEGylated interferon. (1,4).

Starting with 2013, direct acting antiviral (DAA) substances have become available (Fig. 1), which in diverse combinations have proved 85% to 95% efficiency in the treatment of chronic HCV infection, in a much shorter time and with fewer notable adverse effects, especially when compared with the standard PegInterferon + Ribavirin treatment. In 2015, direct acting antiviral treatments became available for use in Romania through the National Health Insurance Services programs, but with the expense being settled only in cases of liver cirrhosis level of HCV infection (fibrosis score of F4). This therapeutic variation (interferon free) involves the association of VIEKIRAX® (Ombitasvirum + Paritapresvirum + Ritonavirum) and EXVIERA® (Dasabuvirum), with the association of RIBAVIRINA in some cases.

MATERIALS AND METHODS

During the years 2011 to 2016, Victor Babes Infectious and Tropical Diseases Hospital was involved in a research project (PN II PT PCCA 88-2011), coordinated by the Cantacuzino National Institute of Research in partnership with Fundeni Clinical Institute, St Nicolau National Virology Institute and Personal Genetics SA, with the purpose of optimizing the current standard treatment for HCV infected population. The project targeted the identification of genetic markers resistant to PegInterferon and Ribavirin for the development of an algorithm to optimize treatment indication, especially considering the numerous adverse effects of the treatment and the major impact on patient quality of life. At Victor Babes Hospital, we've created a database of 190 patients treated and closely monitored between 2012 and 2014, with the analysis of evolution to treatment – virusologic response and its adverse effects.

The ongoing project had a temporary superposition over the period of research and implementation into current practice of DAA. Thus, the project presents a comparative study of the two types of treatment, using the research developed in our study, for the same category of patients – chronic HCV infection in level F4 fibrosis.

It is an observational retrospective study over two groups of patients treated and monitored from 2012 to 2016. The criteria for the inclusion in the study were as follows: F4 level fibrosis, measured through approved National Health

Insurance Services procedures (Fibroscan® as well as Fibroscore®), PegInterferon and Ribavirin treatment (group A) and DAA treatment respectively (group B). The criteria for treatment efficiency applied to the studied groups were SVR in both groups. An added criterion was the percentage of associated adverse reactions to the selected treatment. The collection, processing of data and execution of graphs were done in Excel v.2010.

RESULTS AND DISCUSSIONS

The number of patients with F4 stage fibrosis treated with PegInterferon and Ribavirin was 24 in a period of 2 years (2012 to 2014) and the number of patients treated with DAA was 89 in a period of 1 year (2015 to 2016).

Table 1. *Comparative aspects between the two groups of F4 patients*

Characteristic	Group A (n=24)	Group B (n=89)
Average age (years)	56.8	60.6
Gender (M/ F)	14/10	52/37
Undetectable viral load at the end of treatment	2 (8%)	87 (98%)
Haematological adverse reactions		
Neutropenia	19 (79%)	0 (0%)
Thrombocytopenia	11 (46%)	0 (0%)
Anaemia	20 (83%)	18 (20%)

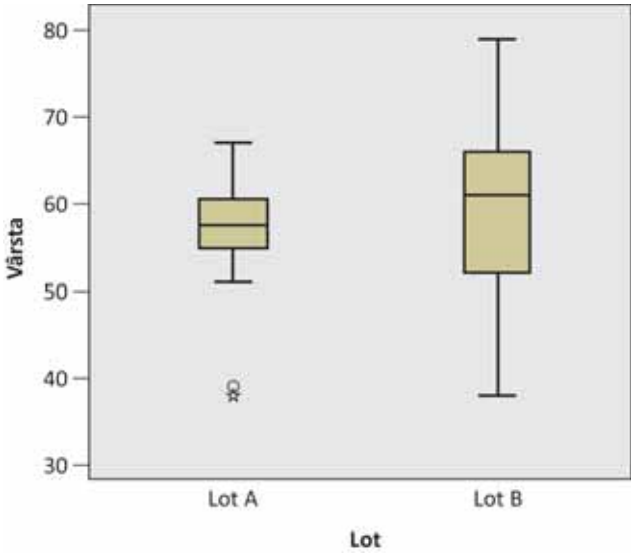

Figure 2. *Average age in both groups*

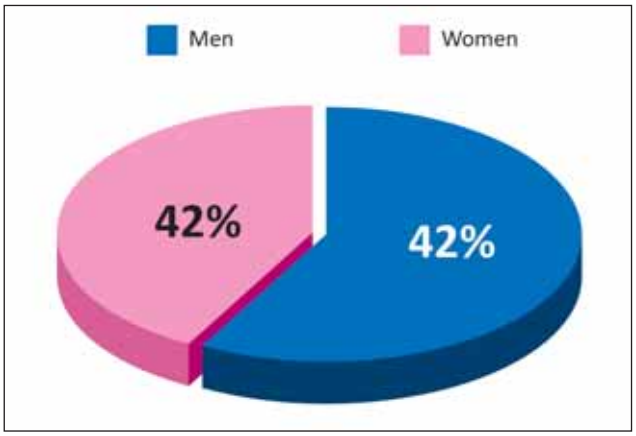

Figure 3. *Gender distribution in group A*

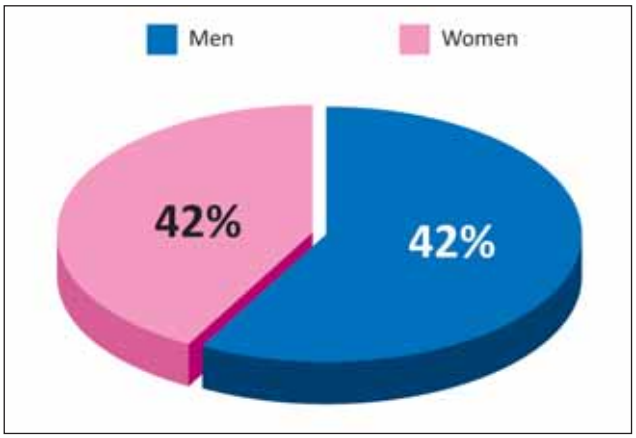

Figure 4. *Gender distribution in group B*

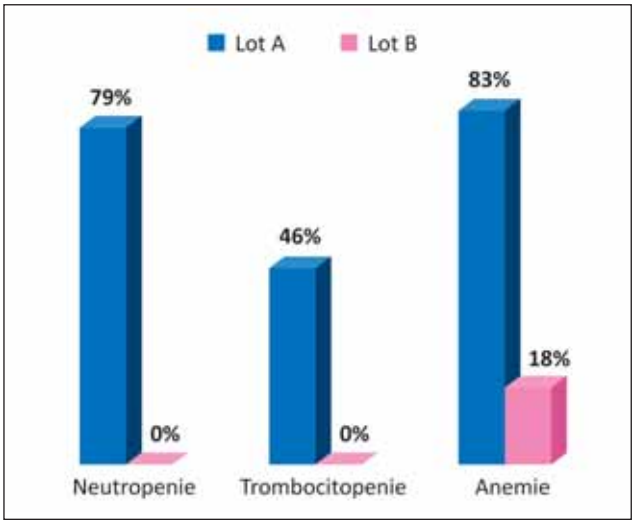

Figure 5. *Percentage of adverse effects in the two groups*

The average age was approximately 57 in group A compared to 61 in group B (Fig. 2). The gender ratio was balanced with 42% women and 58% men in both groups (Fig. 3,4).

In regards to undetectable viral load measured at the end of treatment period, 8% (2 patients) registered in group A, and 98% (87 patients) in group B respectively (Table 1) (Fig. 1).

When it comes to haematological adverse reactions, a much lower rate was observed in group B compared with the higher rate in which these effects appeared in group A (Table 1) (Fig. 5).

Besides the haematological adverse effects, other involved effects were:

- **In group A:**
  - Malaise (67%);
  - Depression and other psycho-social reactions (58%);
  - Thyroiditis with hypo/hyperthyroidism (36%);
  - Weight loss and loss of appetite (79%).
- **In group B:**
  - Malaise (28%);
  - Depression (17%);
  - Jaundice (4%);
  - Acute renal failure with associated haemodialysis and treatment cessation – one patient;
  - Death (one patient; 3 days after the end of treatment).

CONCLUSIONS

1. DAA based treatment is superiorly efficient to PegInterferon and Ribavirin treatment in HCV infected populations with F4 stage liver fibrosis;
2. Fewer side effects appeared less frequently in group B (DAA) than in group A;
3. The introduction of DAA molecules for patients with HCV liver cirrhosis – F4 fibrosis has permitted better access to treatment for this particular category of patients through the lowering of both treatment period and the number of adverse effects;
4. The adverse effects of specific to DAA, drugs with a short history of use in clinical settings, needs close monitoring in the population group during as well as 3 months after the end of treatment.

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