

Concordance of non-invasive tests for liver fibrosis in HCV patients proposed for treatment with direct acting antivirals

Andreea Cazan^{1,2}, Catalin Dutei³, Ioana Husar-Sburlan³, Vasile Balaban¹, Maria Ispas^{1,3}, Mihaela Barbu³, Oana Balas³, Boroka Horeanga³, Denisa Oprisanescu³, Mircea Diculescu^{1,3}, Emanoil Ceausu^{1,2}, Petre Iacob Calistru^{1,2}, Mircea Manuc^{1,3}

¹“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

²Clinical Hospital of Infectious and Tropical Diseases “Dr. Victor Babes”, Bucharest, Romania

³Fundeni Clinical Institute for Digestive Diseases and Liver Transplant, Bucharest, Romania

ABSTRACT

With the introduction of direct acting antivirals in the therapeutic armamentarium of hepatitis C (HCV), policy makers have set criteria for treatment eligibility. In Romania, the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir is reimbursed for F4 fibrosis on liver biopsy/Fibromax, or F3 with contraindication to interferon (IFN). Our aim was to assess treatment eligibility and discordance between serological, elastometric and imaging evaluation of fibrosis in a cohort of patients with HCV.

We evaluated both newly diagnosed and previously known HCV patients with advanced fibrosis, from our database, during a period of 7 months, between November 1st, 2015 and May 31st, 2016. Clinical, biological, ultrasound, elastography and endoscopy data were collected.

Altogether 146 patients were assessed for treatment eligibility. Among them, 61% were females, with a mean age of 60 ± 8 years. Regarding treatment status, 52.5% were naive, 27.4% nonresponders, 17.81% relapsers and 2.74% intolerant to bitherapy. 54.8% had elevated alpha-fetoprotein and were checked by advanced imaging for exclusion of hepatocellular carcinoma (HCC) – of them, 8 were diagnosed with HCC. On ultrasound, almost 1/2 patients had dilated splenoportal axis and at endoscopy 42% had esophageal varices. Transient elastography (Fibroscan) was done in 88/146 patients: 82.95% were F4, 1.14% F3-F4, 9.09% F3 and 6.82% <F3; 125/146 underwent biomarker evaluation of fibrosis: 78.4% were F4, 3.2% F3-F4, 11.2% F3 and 7.2% <F3; 20% of patients had significant steatosis (S \geq 2). On discordance analysis of the fibrosis evaluation methods, 7 cases had low fibrosis on serum markers but advanced fibrosis on elastography. All had genotype 1b, except for 2 patients (one G2 and the other G3) and the mean viremic load was 1,812,994 UI/ml. Reasons for ineligibility were: HCC (8/146), decompensation (9/146) and <F4 fibrosis without arguments for cirrhosis or contraindication for interferon treatment.

Keywords: chronic HCV infection, liver fibrosis, direct acting antivirals

INTRODUCTION

HCV chronic infection is a worldwide health problem, 170 millions of infected persons being reported in 2015 (before the routinely use of direct acting antivirals). In 2018, the World Health Organization reports 71 millions infected persons globally.

The infection is often asymptomatic, having a rate of chronicization of approximately 67%. The

interval from the moment of the infection to development of cirrhosis or hepatocellular carcinoma can vary between 20 to 40 years (rate of progression from chronic hepatitis to cirrhosis being approximately 27,9%) (1).

HCV infection is associated with high rates of morbidity and mortality, through associated complications: systemic involvement, advanced liver fibrosis and cirrhosis and hepatocellular carcinoma,

Corresponding author:

Prof. Petre Iacob, MD, PhD

E-mail: pcalistru@yahoo.com

Article History:

Received: 10 September 2018

Accepted: 24 September 2018

with high costs for health systems. Before evolving to advanced fibrosis, chronic hepatitis C can produce extrahepatic diseases (diabetes mellitus type 2, cryoglobulinemia, neurological and cardiologic involvement), altering the patients quality of life.

First therapeutical interventions (interferon, pegylated interferon, ribavirine) are associated with cure rates varying between 35-66% (2). Later on, the addition of first generation of protease inhibitors (telaprevir / boceprevir) increased the rate of sustained virological response (with almost 20% comparing with bitherapy), but with the price of some adverse events, added to already known and difficult to manage adverse events associated with bitherapy (3). The existence of new generation of direct acting oral antivirals raised significantly the cure rates, simultaneously with reducing the adverse events. One of the few limitations of this treatment represents the costs.

Once with the introduction of new antivirals in the therapeutic arsenal of chronic hepatitis C, the eligibility criteria have been established. At the end of 2015, in Romania the antiviral combination ombitasvir / paritaprevir / ritonavir with dasabuvir had been approved for patients with severe fibrosis (F4 stage, compensated liver cirrhosis – Child Score A), confirmed by Fibromax or liver biopsy (4).

The noninvasive tests for stadialisation of liver fibrosis replaced with succes the gold standard method - the liver biopsy. Despite the high specificity and sensitivity, these tests can be discordant and the interpretation can be a real challenge when is necessary to establish the eligibility for direct antiviral treatment.

The european and american guidelines, but also our nation protocol (elaborated by the National Health Insurancy Institution) recommend that patients with chronic hepatitis C to be evaluated using a noninvasive test for liver fibrosis stadialisation, for monitoring but also for treatment access (4-6).

The aim of this study was to evaluate the eligibility to treatment, but also the concordance between serological, elastographic and imaging tests for liver fibrosis in a group of patients with hepatitis C.

MATERIALS AND METHODS

We evaluated new diagnosed, but also already known patients with chronic hepatitis C with ad-

vanced fibrosis (the latest from our data base), during 7 months interval, between 1st november 2015 and 31st may 2016. We collected clinical, biological (including noninvasive serological markers for fibrosis – Fibromax), ultrasonographical, elastographic and endoscopical data, that have been introduced in a new data base. These data were statistical analysed using Excel and EpiInfo programs.

RESULTS

We evaluated 146 patients for eligibility to treatment with direct acting antivirals. 89 (61%) were women and 57 (39%) were men, with a mean age of 60 ± 8 ani.

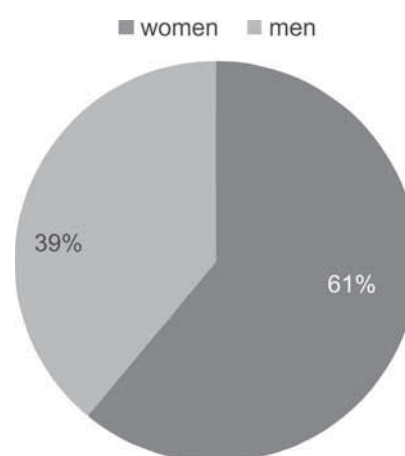


FIGURE 1. Gender distribution in our cohort

Regarding the previous therapies, 58 (52.5%) were naïve, 30 (27.4%) nonresponders, 19 (17.81%) relapsers and 3 (2.74%) with intolerance to bitherapy (figure 2).

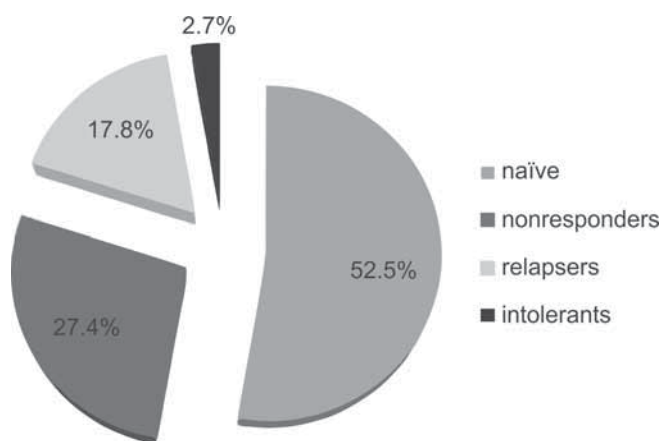


FIGURE 2. The patients status regarding previous antiviral therapies

80 patients (54.8%) presented elevated levels of alpha fetoprotein (figure 3), being imagistically

evaluated for hepatocellular carcinoma exclusion – from all of them, 8 were diagnosed with hepatocellular carcinoma.

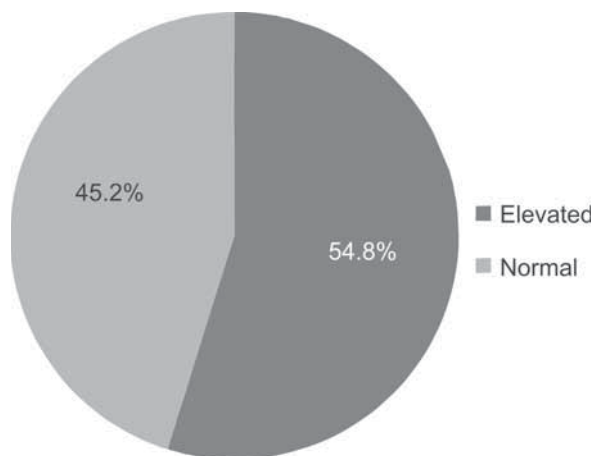


FIGURE 3. Alfa fetoprotein values in our cohort

The diagnosis of portal hypertension requires invasive measurements (catheterizing the inferior vena cava and right hepatic vein to measure the pressure gradient between portal vein and inferior vena cava) so we used some surrogates noninvasive markers (like abdominal ultrasound), and also endoscopic evaluation for identifying patients with advanced portal hypertension (searching for esophageal varices). On liver ultrasound, almost half of patients had dilatation of portal system, and on upper gastrointestinal endoscopy 61 (42%) had esophageal varices.

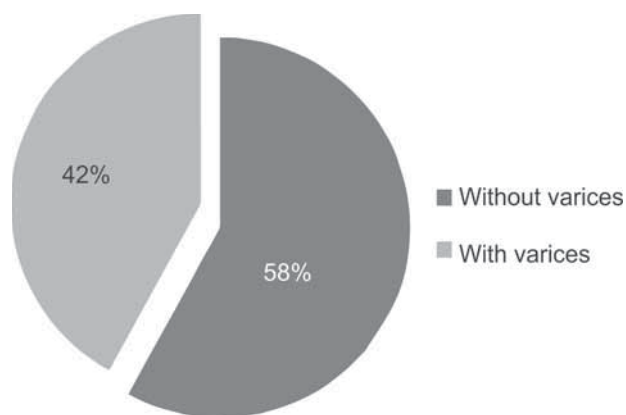


FIGURE 4. Esophageal varices on endoscopic screening

The transient elastography (Fibroscan) was performed in 88/146 (60.27%) patients: 73 (82.95%) have F4 fibrosis, one (1.14%) F3-F4 fibrosis, 8 (9.09%) F3 fibrosis and 6 (7.2%) <F3 fibrosis; 20% of patients had important steatosis (S≥2).

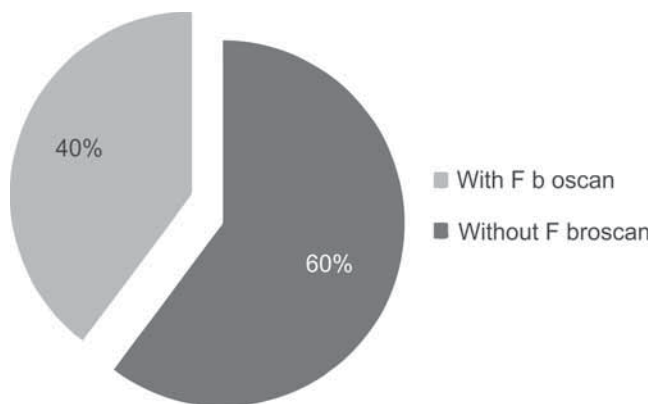


FIGURE 5. Transient elastography (Fibroscan) in our cohort

At concordance analysis regarding the noninvasive tests used for stadialisation of liver fibrosis, 7 (7.95%) patients had mild fibrosis on serological markers, but advanced on elastography; for 4 of them the antiviral treatment was approved based on another criteria of portal hypertension, anterior proves for advanced fibrosis, but also on comorbidities existence. In our cohort, 80% of patients were eligibles for treatment. All patient had genotype 1b, except for two of them (one with G2 and another with G3), mean viral load being 1,812,994 UI/ml. The noneligibility arguments were represented by: presence of hepatocellular carcinoma, decompensated cirrhosis or fibrosis stage <F4 (without arguments for cirrhosis or contraindication for interferon therapy).

DISCUSSION

Liver biopsy is considered the gold standard for hepatic liver diseases (including stadialisation of fibrosis), but nonvasive tests have been used on a great scale, with good results. Taking into consideration that liver biopsy can not offer a specificity and sensitivity of 100%, it is unanimously accepted that surrogate noninvasive tests will give results inferior to liver biopsy, but similar.

The discordant results obtained by two different noninvasive tests at the same patient regarding severity of fibrosis represents sometimes a barrier to access the antiviral therapy. On the other hand, using a single test for evaluation can omit some patients from treatment program. Searching for other severity criteria (presence of esophageal varices, ultrasonographic criteria for portal hypertension) will allow these patients to benefit from new antiviral

treatment. A comparative study on 183 patients with chronic HCV infection revealed that the best diagnostic performance had the association of Fibroscan and Fibrotest, with ROC curves 0.88 for $F \geq 2$, 0.95 for $F \geq 3$ and 0.95 for $F = 4$. When the two results were concordant, the biopsy confirmed it in 84% for $F \geq 2$, 95% for $F \geq 3$ and 94% for $F = 4$. The conclusion of the study was that the association between two noninvasive tests can avoid the liver biopsy in the majority of patients with chronic HCV infection (12). Despite these results, using two tests on great scale is not cost-efficient. When we have to do with discordant results, the recommendation is, for the benefit of the patient, to be taken into consideration the most severe result, and the patient to be treated and monitored based on that result.

CONCLUSIONS

In our cohort we had a big rate of patients having eligibility criteria for new treatment with direct acting antivirals. The elevated percent of naive patients reflects a low acceptability for interferon based therapy, but also a late diagnostic, in advanced stages of the disease. The discordance rate between noninvasive tests was low in our group. In patients with discordant results, the more severe stage of fibrosis was taken in the account, searching for others criteria for initiating the antiviral treatment with the combination approved, for a correct selection.

REFERENCES

- Pagliaro L, Peri V, Linea C et al. Natural history of chronic hepatitis C. *Italian Journal of Gastroenterology and Hepatology* (01 Jan 1999, 31(1):28-44)
- Foster GR. Pegylated interferons for the treatment of chronic hepatitis C: Pharmacological and clinical differences between peginterferon-alpha-2a and peginterferon-alpha-2b. *Drugs*. 2010;70(2):147-65
- Matthew J Akiyama, Joy I Piotrowski, Marina M Roytman et al. New Triple Therapy for Chronic Hepatitis C: Real Life Clinical Experience in a Community Setting. *Hawaii J Med Public Health*. 2013 Sep; 72(9 Suppl 4): 6–13
- CNAS, Protocol J05AX66
- Non-invasive tests for evaluation of liver disease severity and prognostic, EASL, 2016
- HCV testing and linkage to care, AASLD, IDSA, 2017
- EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis
- J. Chan, N. Gogela, H. Zeng et al. Direct acting antiviral therapy for chronic HCV infection results in liver stiffness regression over 12 months post-treatment. *Dig. Dis. Sci*, 2017, September
- Gamil M, Alborai M, El-Sayed M et al. Novel scores combining AFP with non-invasive markers for prediction of liver fibrosis in chronic hepatitis C patients. *J Med Virol*. 2018 Jan
- Erman A, Sathya A, Nam A et al. Estimating chronic hepatitis C prognosis using transient elastography-based liver stiffness: A systematic review and meta-analysis. *J Viral Hepat*. 2017 Dec
- Gheorghe L, Iacob S, Curescu M et al. A Real-Life Use of 3 Direct-Acting Antiviral Regimen in a Large Cohort of Patients with Genotype-1b HCV Compensated Cirrhosis. *J Gastrointestin Liver Dis*. 2017 Sep
- Laurent Castera, Julien Vergniol, Juliette Foucher et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatic. *Gastroenterology*, February 2005, Volume 128, Issue 2, Pages 343–350