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Review

The evaluation of liver fibrosis regression in chronic hepatitis C patients after the treatment with direct-acting antiviral agents – A review of the literature

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Abstract

The second-generation of direct-acting antiviral agents are the current treatment for chronic viral hepatitis C infection. To evaluate the regression of liver fibrosis in patients receiving this therapy, liver biopsy remains the most accurate method, but the invasiveness of this procedure is its major drawback. Different non-invasive tests have been used to study changes in the stage of liver fibrosis in patients with chronic viral hepatitis treated with the second-generation of direct-acting antiviral agents: liver stiffness measurements (with transient elastography or acoustic radiation force impulse elastography) or different scores that use serum markers to calculate a fibrosis score. We prepared a literature review of the available data regarding the long-term evolution of liver fibrosis after the treatment with direct-acting antiviral agents for chronic viral hepatitis C.

Keywords : chronic viral hepatitis C, direct-acting antiviral agents, liver fibrosis

Highlights

- ✓ Transient elastography is the routine investigation for liver fibrosis monitoring in patients with chronic viral hepatitis C treated with direct acting antiviral agents.
- ✓ The APRI and FIB-4 scores registered the highest decrease between the baseline and the end of the treatment in patients with chronic viral hepatitis C treated with direct acting antiviral agents.

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Introduction

The main objective in treating chronic viral hepatitis C (CHC) with the second-generation of direct-acting antiviral agents (DAAs) is to achieve a sustained virologic response (SVR). Reversing liver fibrosis in previously infected patients is a secondary goal, since achieving viral clearance does not reverse all the liver damage. DAAs do not have an anti-fibrotic effect (1). In patients who achieved SVR with interferon therapy (the previous standard of care in CHC), liver fibrosis regression was measured in 42% of the cases, while 53.1% of the patients did not have a significant change in the liver fibrosis stage, and fibrosis progression was reported in 4.6% of the patients (2).

In order to measure liver fibrosis, besides the gold standard of liver biopsy, various fibrosis scores calculated from routine laboratory tests have been developed and validated in recent years. These scores have numerous advantages, as they are neither invasive procedures nor expensive investigations. The aim of this article is to assess the changes that occur in liver fibrosis after SVR is achieved with DAAs, measured through liver biopsy and different non-invasive tests: transient elastography (TE), acoustic radiation force impulse elastography (ARFI), fibrosis-4 score (FIB-4), aspartate aminotransferase-platelet ratio index (APRI), and hyaluronic acid (HA).

Discussions

Transient Elastography (TE)

TE represents a non-invasive method of liver stiffness (LS) measurement which is used for fibrosis screening in various hepatic disorders as an alternative to liver biopsy (3). TE is routinely performed for liver fibrosis assessment prior to DAA therapy and also as a follow-up after achieving SVR (4-6).

A cohort study including adults with CHC who received DAA-based therapies reports a regression of >30% in LS measured by TE 12 months after the end of treatment (EOT) (7). Fibrosis regression was demonstrated in another study including patients with advanced fibrosis (F3-F4), who were monitored by TE at baseline, at EOT, and 12 weeks and 24 weeks after EOT (8). There were significant differences registered by TE between the baseline and EOT (8.3 kPa vs 7.4 kPa), EOT and 24-week SVR (7.4 kPa vs 5.3 kPa), and baseline and 48-week SVR (8.3 kPa vs 5.4 kPa) (9).

An improvement of LS was noticed in 82% of the patients with SVR at a 2-year follow-up. In 42% of the cases, liver fibrosis was decreased by at least 3 kPa (10). Facciorusso et al. found an LS decrease from 12.3 kPa to 6.6 kPa at a 5-year follow-up after DAA therapy (11).

Another study with a long follow-up period (up to 72 weeks after EOT) indicated a significant and steady decline in LS values. The median LS values were 11.25 kPa before the initiation of treatment, 7.8 kPa at EOT, 6.45 kPA at 24 weeks of SVR, 6.25 kPa at 48 weeks of SVR, and 5.45 kPa at 72 weeks of SVR (12). In patients with liver cirrhosis, a large decrease in LS was observed, from a 32.5 kPa median at baseline to a 21.3 kPa median at EOT (13).

APRI

APRI is a simple-to-use liver fibrosis marker, calculated by applying the following formula: [Aspartate aminotransferase level (ULN)/platelet count (109/L)] ∗100 (14). The APRI test has a 65.1% sensitivity (Se) and 7l.8% specificity (Sp) in detecting F2-F3, and 93.8% Se and 72.4% Sp in diagnosing liver cirrhosis. An APRI value of 0.77 differentiates F1 and F2, and a value of 0.84 is the cut-off between F3 and F4 (14, 15). APRI values decrease in CHC patients after treatment with DAAs, even in subjects who do not achieve SVR. In patients with SVR, the median APRI was lowered from 1.07 to 0.41. In non-SVR patients, the median value dropped from 2.05 to 1.13 (5). In another study, 48% of the patients had an APRI score higher than 1 at baseline, but after DAA treatment, only 7.7% had APRI values above 1 (16).

Median APRI values decrease significantly after 24 weeks of DAA therapy, from 1.4 to 0.5. After this period, the APRI stabilizes, and at 96 weeks after EOT no significant change is observed (17). Lledó et al. reported that the APRI index was decreased at EOT, but there was no significant variation in its values at 12-week SVR follow-up: 1.47 at baseline, 0.58 at EOT, and 0.54 at SVR (18). APRI regression is found in patients with liver transplant treated with DAAs (from 2.7±0.3 to 0.4±0.05 at 12-week SVR). Patients with severe inflammation or liver steatosis at baseline have greater improvements in the APRI index compared to those with lower inflammation and no steatosis (19). In the study conducted by Fabbri et al., APRI decreased in hepatitis C/HIV co-infected patients who underwent treatment with DAAs from a median of 0.94 to 0.37 (20).

Improvements in the APRI score after CHC treatment are explained by the normalization of liver enzymes and the increase in the number of platelets. Patients with F2-F3 have an improvement in APRI regardless of their treatment response. In patients with cirrhosis, fibrosis regression is significantly correlated with achieving SVR (21). In a study by Christian et al., the reduction in APRI was found

to be more pronounced in patients with F0-F2 compared to F3-F4 (22).

Tao et al. studied liver fibrosis regression in CHC patients infected with the genotype 3 variant of hepatitis C virus, treated with 3 different DAA regimens. This particular viral genotype has a faster progression of liver fibrosis to cirrhosis and shows more resistance to DAAs. A significant reduction in APRI was found after different DAA treatments, both in respondents (from 1.834 to 0.619, $p < 0.001$) and non-respondents (from 5.026 to 1.248, $p = 0.002$ for relapsed patients) (23).

Serum markers of liver fibrosis

Different serum biomarkers have been studied for the detection of liver fibrosis.

Hyaluronic acid (HA) was demonstrated to be useful for the detection of liver fibrosis in CHC patients, especially in cases where liver biopsy is restricted (such as end-stage renal disease) (24, 25). CHC patients who responded to treatment with daclatasvir and asunaprevir had a lower value of HA at SVR compared to the baseline values (123 ± 43 vs. 71 ± 14 ng/mL, $p<0.01$), while non-respondents showed no significant difference before and after the treatment (145 ± 43 vs. 172 ± 46 ng/mL, $p = 0.465$) (26). The Enhanced Liver Fibrosis (ELF) score is an algorithm that uses age and serum levels of procollagen type III amino terminal propeptide, tissue inhibitor of metalloproteinases-1 and HA to give an estimate for liver fibrosis. In a sofosbuvir treatment study, the ELF score was decreased compared to the baseline (from 10.00 to 9.37, $p=0.007$). Patients treated with sofosbuvir and pegylated interferon showed a temporary increase in HA measurements at 4 weeks during the treatment (from 59.5 to 177.9 mg/ml, $p=0.002$), presumably because of the pro-inflammatory effect associated with the interferon therapy (6).

FIB-4

The FIB-4 score has been established alongside other non-invasive fibrosis scores in the international guidelines for the evaluation of liver fibrosis (15). The Apricot study developed a simple test using laboratory measurements to predict liver fibrosis in a large cohort of HIV/hepatitis C co-infected patients. The results of the study showed that age, serum aspartate aminotransferase, international normalized ratio, and platelet count were independent predictors of fibrosis. These variables were used to obtain the following formula: Age (years) × aspartate aminotransferase [U/L] / (platelets [109/L] × (alanine aminotransferase [U/L])1/2), known today as the FIB-4 index (27). In a recent study on a multicenter real-world cohort, significant liver fibrosis and cirrhosis were predicted with high accuracy by FIB-4 using TE as a reference (28).

FIB-4 has been validated for the evaluation of CHC and has acceptable Se and Sp, particularly in advanced fibrosis and cirrhosis. FIB-4 shows a significant decrease in all patients undergoing DAA treatment, especially in those achieving SVR ($p<0.001$) (5). A significant decline in FIB-4 values is seen from baseline to 24 weeks after SVR ($p<0.0001$) (11).

Another study proposed that a longer follow-up period could allow detection of LS changes unrelated to the decrease in the liver inflammatory activity, but rather associated with the improvement in liver architecture and function. Giannini et al. followed up 52 CHC patients for a median of 60 weeks after successful DAA treatment with SVR. FIB-4 values progressively decreased from baseline to the end of the follow-up period (16).

ARFI

ARFI is a novel procedure that enables the assessment of liver fibrosis during a conventional ultra-sonographic examination. This imaging technique quantifies the mechanical properties of tissues, without manual compression, by measuring the shear wave velocity induced by acoustic radiation and propagation in the liver tissue (29). Compared to TE, the elastography technique currently used in clinical practice, ARFI showed promising results in the assessment of liver fibrosis staging in CHC and HIV/hepatitis C co-infected patients (13, 30). Similar to other studies on patients with SVR after DAAs, the ARFI evaluation found that LS improves in patients with cirrhosis. Also, a decrease in LS was detected at 24 weeks after SVR by ARFI similar to TE (from 2.04 ± 0.62 m/s at baseline to 1.75 ± 0.57 m/s at 24 weeks after SVR) (31).

Liver biopsy

The degree of inflammation, the stage of fibrosis, and the histological improvement after achieving SVR are still best evaluated through liver biopsy (32). In addition to these findings, a recent short-term study evaluated 51 patients who underwent liver biopsies after SVR was achieved. Although liver enzymes normalized after achieving SVR, significant histological inflammation was still present in 16% of the patients (33).

Jason et al. tried to assess whether TE can be used in the management of patients with advanced fibrosis or cirrhosis, after achieving SVR, and compared the results to liver biopsy. In their study, there was discordance between post-SVR fibrosis stages predicted by TE vs. liver biopsy. Thus, it is unclear if TE following SVR can predict the fibrosis stage as reliably as liver biopsy (34).

Conclusions

TE has become a routine investigation for liver fibrosis monitoring in patients receiving treatment with DAAs, ARFI being another elastography method that can be used. The APRI and FIB-4 scores registered the greatest change when measured at EOT, since the platelet count and the liver aminotransferase values that make up their formulas showed the most significant improvement around that point. Serum markers such as HA, tissue inhibitor of metalloproteinases-1, and the combined ELF score also improve after the treatment with DAAs.

Acronyms and abbreviations

APRI – aspartate aminotransferase-platelet ratio index
ARFI – acoustic radiation force impulse elastography
CHC – chronic viral hepatitis C
DAAs – direct-acting antiviral agents
EOT – end of treatment
FIB-4 – fibrosis-4 score
HA – hyaluronic acid
LS – liver stiffness
Se – sensitivity
Sp – specificity
SVR – sustained virologic response
TE – transient elastography.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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