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REVIEW ARTICLE

Why do I treat my patients with mild hepatitis C?

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Abstract

The major advances achieved in the treatment of HCV by the development of new direct-acting antiviral agents (DAAs) allow treatment of almost the entire spectrum of patients with chornic infection. As a result of the exceedingly high cost of DAAs in many countries, IFN-free DAA regimens are mostly reserved to patients with advanced fibrosis or cirrhosis. Hence, treatment of patients with milder liver disease is often deferred. This could ultimately result in an increased burden of advanced liver disease and in increased long-term costs of management. Moreover, studies performed during the 'interferon era' and the early data on interferon-free regimens show that patients without severe fibrosis achieve higher rates of sustained virological response with less treatment-related adverse events. Unfortunately, there is no univocal way to predict the progression of liver fibrosis and therefore to identify the patients with early disease who would require urgent HCV treatment. Many studies have also demonstrated that treatment-induced HCV clearance reduces all-cause mortality regardless of the stage of liver fibrosis, pointing to an effect on extrahepatic manifestations of HCV infection. Last but not least, pharmacoeconomic studies show that DAA treatment of patients with mild HCV disease is cost-effective even at high prices of drugs, thus suggesting the opprtunity to treat regardless of the stage of liver disease.

Keywords
antiviral agents – chronic hepatitis C – costs – extrahepatic manifestations

Chronic hepatitis C may eventually progress to cirrhosis, liver decompensation and hepatocellular carcinoma and many studies proved that HCV eradications reduce the risk of developing liver complications (1). Moreover one multicenter international study has already demonstrated that achieving SVR reduces not only liver related but also all-cause and non-liver-related mortality (2).

The availability of new direct-acting antiviral agents (DAAs) have changed the scenario of HCV treatment but the high costs of these regimens caused relevant restrictions of access to the drugs. Patients with early fibrosis stages will not have access to the new therapies and this will increase the risk to development of severe liver fibrosis, of hepatocellular carcinoma and liver decompensation.

When we delay the antiviral treatment in patients with chronic HCV-related mild hepatitis we need to taking into account the following issues (Fig. 1):

- Unpredictable course of liver disease at individual level (influence of cofactors)
- Patients with mild fibrosis are 'easy to treat'
- HCV eradications as cure of extrahepatic complications
- Pharmacoeconomic considerations

Unpredictable course of liver disease at individual level (influence of cofactors)

In the last years, a lot of studies have tried to identify patients at early disease stages but high risk of fibrosis progression. Indeed, recognizing the cofactors that contribute to disease progression among HCV patients may ameliorate treatment approaches and overall disease management. Many studies have focused on the impact of obesity and metabolic disorders on the natural history of chronic HCV and as is already known, the effects

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Key points

- The impact of clinical, metabolic and genetic factors which are associated with liver fibrosis in chronic HCV patients is still controversial, and the progression of disease remains largely unpredictable.
- The majority of patients with immunological driven extrahepatic complications as Mixed cryoglobulinemia and Non-Hodgkin Lymphoma had complete resolution with successful HCV clearance.
- Viral eradication is able to reduce the risk of cardiovascular and metabolic disease and also of non-liver related mortality.
- Pharmacoeconomic analysis confirmed that IFN-free regimens are more cost-effective that IFN-based therapy for all HCV patients.

of diabetes mellitus, metabolic syndrome and nonalcoholic fatty liver disease (NAFLD) have been related to the progression of hepatic fibrosis (3). However, the impact of the those factors on progression of disease among chronic HCV patients is still controversial because of conflicting results of existing studies (4, 5).

Data from literature have shown that oestrogens exert a beneficial effect on liver disease by slowing the progression of fibrosis (6) and Villa *et al.* (7) have recently demonstrated that the progression of fibrosis in women is a discontinuous process: very slow during reproductive age and rapid after menopause. The authors have found that the severity of liver necroinflammation and fibrosis, was very low in women of reproductive age and in premenopausal ones while it increase among early menopausal women and became very higher among late menopausal women. Furthermore, the levels of circulating estradiol was found independently related with severe fibrosis.

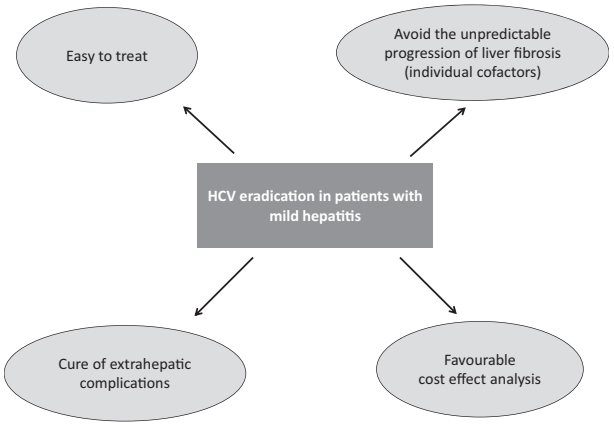

Fig. 1. Main indications of HCV antiviral therapy in patients with mild liver disease.

In another study (8), the same group have also found that the more pronounced inflammatory state associate to the more rapid progression to fibrosis resulted in an higher resistance to antiviral therapy. This suggests that CHC in women should be treated early, regardless the fact that they have mild liver disease, as this condition will last only as long as the oestrogen-exposed period and the progression to a severe liver fibrosis remains not predictable.

Both European and US guidelines reccomend (9, 10) to prioritize the treatment of patients with HIV or HBV coinfection regardless of the fibrosis stage.

Indeed, whereas treatment of HIV with ART appears to slow the progression of liver disease, coinfected patients remain at greater risk for HCV disease progression than patients with HCV monoinfection (11). In the era of several new DAA combination therapies, treatment response rates no longer differ between HIV/HCV-coinfected and HCV-monoinfected patients; Therefore, in countries with access to the new DAAs, interferon-free DAA-containing treatment is strongly recommended for those patients and the antiviral regimen should be selected based on HCV genotype and according to current guidelines as drug–drug interactions between cART, ribavirin, and especially the new HCV protease inhibitors. A careful selection of both HIV and HCV drugs is required as well as close monitoring. Also in patients with HBV coinfection the HCV antiviral treatment should be performed with the same rules as applied to HCV-monoinfected patients. However, there is a potential risk of HBV reactivation during or after HCV clearance (12) and if HBV replication is detectable at a significant level, HBV nucleoside/nucleotide analogue therapy is indicated. Potential drug–drug interaction have been shown between simeprevir and tenofovir. Therefore, in patients receiving tenofovir as anti-HBV treatment, the eGFR and tubular function should be monitored frequently during treatment and tenofovir dose adjustment may be necessary.

Recent genome-wide association studies (GWAS) have highlighted several genetic polymorphisms as predictive risk factors of rapid fibrosis progression in chronic hepatitis C (13–15). Interleukin 28B (IL28B) genotype may be associated with fibrosis progression after interferon-based therapy, although the results of recent studies remained inconclusive (13). More recently, a series of SNPs [MERTK (rs4374383), TULP1 (rs9380516), GLT8D2 (rs2629751) and RNF7 (rs16851720)] have been identified as susceptible genetic alterations for HCV-related liver fibrosis (16), and other studies have proposed SNPs at rs738409 in adiponutrin/patatin-like phospholipase domain-containing 3 (PLPNA3) as genetic determinants of liver fat content, disease progression and fibrosis in nonalcoholic fatty liver disease (NAFLD) and in chronic hepatitis C (17–19). However, most of these results require verification,

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and whether the combined use of these genetic predictors can assess the risk of fibrosis progression in patients with HCV after antiviral therapy remains unclear.

Easy to treat

The severity of liver disease with extensive fibrosis or cirrhosis, was identified as important additional determinants of the SVR in IFN-α/ribavirin-based regimens (20, 21).

Even if the new antiviral drugs are much less influenced by host or viral parameters and achieve higher cure rates also in patients with severe fibrosis, overall, severe disease is associated with lower SVR rates on both IFN-containing and IFN-free combination regimens (22, 23).

In Neutrino study (22), more than three hundreds patients with HCV genotype 1, 4, 5, or 6, were treated with sofosbuvir combined with peg-interferon and ribavirin. The variables associated with therapy response were cirrhosis, *IL28B* (rs12979860) genotype and ribavirin exposure. The SVR12 for patients with genotype 1 infection was 89.4%, but the SVR12 was inferior in patients with cirrhosis (80%) than in those without cirrhosis (92%). Also in the cohort of 499 patients with HCV genotype 2 or 3 received sofosbuvir and ribavirin, the predictive factors associated with SVR12 were HCV genotype, presence of cirrhosis, HCV-RNA viral load at baseline and ribavirin exposure. The response rates were lower among patients with cirrhosis than for those without cirrhosis (46.9% vs 72.1%).

This is due to a slower second-phase HCV-RNA decline in cirrhotic than in non-cirrhotic patients. The molecular mechanisms underlying the slower infected cell clearance in cirrhotic patients are unknown. It does not appear to be related to different drug exposures in cirrhotics because the first-phase response is identical in cirrhotic and non-cirrhotic patients. Differences in the cirrhotic liver microenvironment might be responsible for differences in the mechanisms of HCV clearance activated in infected cells on efficient antiviral therapy. Treatment duration is a key parameter that can be easily optimized to increase the SVR rates. Stopping treatment too early, before the last infected cell has been cleared or cured, results in reinfection of liver cells, and ultimately, in a virological relapse. In contrast, stopping therapy at any time after the last cell has been eliminated is associated with a definitive cure of infection. Thus, patients with a slow second-phase decline, such as patients with an unfavourable IL28B genotype, cirrhotics, patients infected with HCV genotype 3, etc., need longer therapy than those with a sharp one, regardless of the treatment regimen.

In patients with cirrhosis the use of ribavirin in reccomended. Indeed, Ribavirin accelerates the second-slope of viral decline in a dose-dependent manner in patients in whom virus production is efficiently blocked by IFN-containing or IFN-free drug combinations, through mechanisms that remain debated (24). Thus, ribavirin remains a useful tool to either reduce treatment duration or improve SVR rates and because it is cheap and relatively well tolerated when it is not combined with IFN-α, it remains a very useful tool to anti-HCV treatment regimens and optimize their results. However, the use of ribavirin remains especially challenging in patients with anaemia and concomitant renal impairment and adds both side effects and the need for monitoring to any regimen. Therefore, patients with previous evidence of intolerance to ribavirine should be treated before the development of severe fibrosis to avoid the risk to receive a suboptimal antiviral regimen.

All these considerations clearly suggest that the efficacy of antiviral treatment in patients without mild fibrosis can result higher and that regimens could be shorter with a consequentially reduction in side effects and costs.

Extrahepatic complications

The liver is not the unique organ affected by chronic hepatitis C infection. Indeed, a broad clinical spectrum of extrahepatic complications are associated with this viral infection (25).

In the majority of these associated extrahepatic manifestations, the pathogenic mechanism appears to be immunologically driven, HCV lymphotropism represents the most relevant step in the pathogenesis of virus-related immunological disorders (26). Indeed, infected lymphoid tissue of the host represents a site for the persistence of the HCV infection. HCV exerts a chronic stimulus to the immune system, facilitating the clonal B-lymphocyte expansion and consequent wide autoantibody production, including cryo- and non-cryoprecipitable immune complexes which may lead to organ and non-organ-specific immunological alterations (27).

Mixed cryoglobulinemia (MC) is the most well documented extrahepatic manifestation of HCV infection (26). About 40–60% of HCV-infected patients have circulating cryoglobulins even if only 5–10% of these individuals develop clinical consequences (28). Cutaneous vasculitis with palpable purpura, occurs in one-third of patients ranging from asymptomatic pigmentation to cutaneous ulceration. Renal disease with membranoproliferative glomerulonephritis (GN) occurs in about 30% of patients, ranging from mild proteinuria to progressive renal impairment. Other less frequent symptoms are neuropathy (11–30%), sicca syndrome (10–25%) and arthralgias (35–54%) (29, 30).

This is the reason why in these patients the interferon-based antiviral treatment has been often proposed. The benefit of antiviral treatment on MC related complications had been demostrated with the introduction of peginterferon and ribavirin. With this combinations the rates of SVR increased and follow-up studies

showed that 80–90% of patients had complete resolution of sympthoms with successful viral eradication (31).

However, because of its immune-stimulatory effects, interferon may exacerbate some of the symptoms of MC vasculitis, limiting the tolerability of therapy. Thus, the introduction of interferon-free DAA regimens holds great promise for treating HCV-associated MC.

Similar to MC, even low-grade Non-Hodgkin Lymphoma may respond to antiviral therapy. NHL remission has been reported in a small number of patients treated with interferon-free DAA-based regimens, suggesting that the effect is all virally mediated and not because of anti-proliferative effects of interferon (32). In a Japanese study, HCV therapy seems also able been to reduce the incidence of new onset NHL, making a case for consideration of earlier treatment, even in patients with mild liver disease to prevent future complications (33).

Also in patients with high-grade NHL where a primary treatment of the malignancy is required, the achievement of SVR markedly reduces the risk of NHL relapse (34). suggesting that therapy with DAAs could be given with or even before chemotherapy for high-grade NHL, to improve responses without affect tolerability.

According with these data, patients with evidence of MC, even if with mild liver disease, may represent a population who should be prioritized for early antiviral therapy to prevent future symptomatic vasculitis and lymphoma (30).

In the last years, a lot of studies have shown a higher incidence of cardiovascular and metabolic disorder in patients with chronic HCV infection.

A correlation between HCV infection and atherosclerotic changes has been recently proved and the risk of peripheral artery disease is higher than in uninfected patients (35, 36). Those results suggest that the risk of cardiovascular events and mortality may be elevated among HCV-infected patients and become relevant to assess if eradication of HCV may reduce the risk of cardiovascular disease. A large, retrospective cohort study found that interferon-based therapy significantly reduced stroke incidence compared with no treatment (37). and the long-term extrahepatic benefits of successfully treating HCV infection has been demonstrated also in another recent study where patients with HCV infection treated with interferon-based treatment significantly reduced the incidence of end-stage renal disease, acute coronary syndrome and ischaemic stroke (38).

Data from the literature have shown a higher incidence of type 2 diabetes mellitus with chronic HCV when compared with patients with other liver disorders (25, 39).

Moreover, type 2 diabetic HCV patients had a significantly lower BMI than type 2 diabetic control subjects and significantly higher BMI than non-diabetic HCV patients. In contrast, no association with diabetes mellitus type 1 has been identified (39, 40).

The association between chronic HCV and diabetes mellitus seems to be independent of the severity of the liver disease and is associated with insulin resistance (30, 41).

Insulin resistance correlates with poor outcomes in HCV patients, including accelerated progression of hepatic fibrosis, reduced SVR rates, development of HCC and of type 2 diabetes and its cardiovascular sequelae.

Kawaguchi *et al.* (42), demonstrated that curing HCV with antiviral therapy results in reduced levels of insulin resistance, while levels remain unchanged in virological non-responders. Furthermore a study of an interferon-free, short course of an inhibitor of the HCV non-structural 3 (NS3) serine protease, showed a close correlation between viral load decline and reduction in HOMA-IR levels (43), suggestig that treatment with anti-HCV DAAs may restore insulin sensitivity in chronic HCV-infected patients.

All these evidences confirm that the involvement of non-hepatic organ systems in HCV infection substantially decreases the quality of life of chronically infected patients, and may also increase non-hepatic mortality. Viral eradication reduces extrahepatic manifestations of HCV, and these new regimens which are also better tolerated result strongly indicated for those patients. Not surprisingly, major clinical practice guidelines of international societies have already defined the presence of extrahepatic manifestations as a priority indication for antiviral treatment with DAAs, even in the absence of liver disease (9).

Cost-effect analysis

The global prevalence of hepatitis C virus (HCV) infection, the rate of progression of chronic disease to cirrhosis and liver events and the rapid changing scenario of HCV terapy have lead many groups to perform cost-effect analysis to assess the best strategy of treatment in this setting.

The first study which evaluated the cost effect of Sofosbuvir combined with peg-interferon and ribavirin compared with triple therapy with Bocepevir or Telaprevir, concluded that SOF was cost-effective compared with BOC in all strategies and thus also in patients with mild fibrosis, however, in comparison with TVR-based strategies, SOF was cost-effective in IL28B CT/TT and G1a patients, and not cost-effective in patients with mild or severe fibrosis and in G1b patients (44).

However in a more recent study, Younossi *et al.* (45) compared IFN-free regimens with IFN-based triple therapy and they found that the IFN-free regimens is superior of IFN-based therapy for all G1-HCV patients. Furthermore, they concluded that staging fibrosis in CHC is not cost-effective. Indeed IFN free without staging was more cost-effective than oral IFN-free regimen after staging. This study suggests for the first time that with the achievement of high SVR rates by highly effective IFN-free regimens which caused low side effects and

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that can be administered for shorter duration, the decision to treat or not to treat should not be based on the stage of liver disease.

Similarly, another study have evaluated the cost-effective analysis of sofosbuvir and ledipasvir (46). The authors concluded that treatment not only reduce HCV-related complications but it is cost-effective in the majority of patients.

However, in the conclusion, the authors discuss with major concerns about the possibility to find the immense economic budget to cover the costs of treatment for all HCV treatment-eligible.

Conclusions

In the era of IFN-free regimen with high efficacy rates and better safety profile, treating all HCV patients with IFN-free oral therapy appears to improve outcomes and be more cost-effective. In this review we have analysed the many reasons why we should treat also patients without significant liver damage. Antiviral therapy in patients with mild disease is easier as regimens could be shorter and without combination with ribavirin; HCV eradications significantly reduce the progression of liver fibrosis and acts as cure for the extrahepatic manifestations. Another particular condition in which treatment should be prioritized regardless of the fibrosis stage is the patients who have an high risk of transmitting HCV as active injection drug users, men who have sex with men with high-risk sexual practices, incarcerated persons, persons on long-term haemodialysis, HCV-infected women wishing to get pregnant and healthcare workers who perform invasive procedures. This analysis suggests that liver disease stage-guided treatment protocols should be revisited and that additional resources as well as patient prioritization are needed to manage HCV patients.

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