ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 June 7; 27(21): 2664-2920

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for *WJG* as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2019 is 7.1 and Scopus CiteScore rank 2019: Gastroenterology is 17/137.

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
June 7, 2021

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https://www.wjgnet.com/bpg/gerinfo/242

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World J Gastroenterol 2021 June 7; 27(21): 2771-2783

DOI: 10.3748/wjg.v27.i21.2771

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Direct antiviral agents in hepatitis C virus related liver disease: Don't count the chickens before they're hatched

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Author contributions: Compagnoni S and Bruno EM contributed to the section on relevant concomitant disease; Madonia G contributed to the section on hepatocellular carcinoma; Cannizzaro M contributed to the section on concomitant hepatitis B virus infection; Madonia S contributed to the section on advanced liver disease and coordinated the writing of the paper; All the authors have read and approved the final manuscript.

Conflict-of-interest statement: There is no conflict of interest associated with any of the authors who contributed to this manuscript.

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Abstract

Since molecules with direct-acting antiviral (DAA) became available, the landscape of the treatment of hepatitis C virus (HCV) infection has completely changed. The new drugs are extremely effective in eradicating infection, and treatment is very well tolerated with a duration of 8-12 wk. This review aims to report the outstanding clinical benefits of DAA and to highlight their critical disadvantages, identifying some clinically relevant hot topics. First, do the rates of virological response remain as high when patients with more advanced cirrhosis are considered? Large studies have shown slightly lower but still satisfactory rates of response in these patients. Nevertheless, modified schedules with an extended treatment duration and use of ribavirin may be necessary. Second, does the treatment of HCV infection affect the risk of occurrence and recurrence of liver cancer? Incidence is reduced after viral eradication but remains high enough to warrant periodic surveillance for an early diagnosis. In contrast, the risk of recurrence seems to be unaffected by viral clearance; however, DAA treatment improves survival because of the reduced risk of progression of liver disease. Third, can HCV treatment also have favorable effects on major comorbidities? HCV eradication is associated with a reduced incidence of diabetes, an improvement in glycemic control and a decreased risk of cardiovascular events; nevertheless, a risk of hypoglycemia during DAA treatment has been reported. Finally, is it safe to treat patients with HCV/ hepatitis B virus (HBV) coinfection? In this setting, HCV is usually the main driver of viral activity, while HBV replication is suppressed. Because various studies have described HBV reactivation after HCV clearance, a baseline evaluation for HBV coinfection and a

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Italy

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 22, 2021
Peer-review started: January 25, 2021
First decision: February 28, 2021
Revised: March 26, 2021
Accepted: April 28, 2021
Article in press: April 28, 2021
Published online: June 7, 2021

P-Reviewer: Doganay L, Ristic-Medic D
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Liu JH

specific follow-up is mandatory.

Key Words: Hepatitis C virus; Direct antiviral activity; Advanced cirrhosis; Liver cancer; Diabetes mellitus; Hepatitis C virus/hepatitis B virus coinfection.

Core Tip: The treatment of hepatitis C virus (HCV) infection has changed since direct-acting antivirals (DAAs) became available. DAA use has been extended to patients with advanced cirrhosis and severe comorbidities. Consequently, this review addresses the following questions: What benefits can be expected from eradicating HCV in patients who already have advanced liver disease? Are DAAs associated with an appreciable benefit in liver cancer? Can HCV treatment have favorable effects on the major concomitant disorders such as diabetes or cardiovascular disease? Is there any cause for concern when using DAAs in HCV patients with a concomitant hepatitis B virus infection?

Citation: Compagnoni S, Bruno EM, Madonia G, Cannizzaro M, Madonia S. Direct antiviral agents in hepatitis C virus related liver disease: Don't count the chickens before they're hatched. *World J Gastroenterol* 2021; 27(21): 2771-2783
URL: https://www.wjgnet.com/1007-9327/full/v27/i21/2771.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i21.2771

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, with more than 70 million people infected all over the world[1]. HCV is responsible for many cases of hepatitis, liver cirrhosis, liver cancer (hepatocellular carcinoma, HCC), transplantation (orthotopic liver transplantation, OLT) and liver-related deaths. Initially, all the available treatments were interferon (IFN)-based. However, they were unsatisfactory mainly because the rates of viral response were between 30% and 50%, and their efficacy was strongly dependent on viral genotype and the degree of liver fibrosis. Furthermore, IFN-based treatments had a long duration of 24-48 wk and marked adverse effects limited their use in patients with advanced liver disease and major comorbidities.

More recently, IFN-free treatments with direct-acting antiviral (DAAs) drugs were registered. Their availability has substantially changed the HCV-infection setting. Indeed, DAAs are able to obtain rates of sustained virological response (SVR) higher than 95%, independently of virus genotype or degree of liver damage. They have short duration schedules of 8 wk to 12 wk and are extremely well tolerated[2-4]. More recently, the advent of pangenotypic DAAs has further extended and simplified their use[2,5].

The effects of viral clearance in patients with chronic hepatitis are well known. SVR is generally associated with a biochemical response (normalization of liver enzymes), improvement of liver necroinflammation and reduction in fibrosis progression or regression of fibrosis[6,7].

Due to their efficacy in advanced fibrosis and high tolerability, DAA use has been extended to patients with advanced and even decompensated cirrhosis and patients with severe comorbidities, raising new questions. What benefits can be expected from eradicating HCV in patients who already have advanced liver disease? Is DAA-induced SVR associated with an appreciable benefit in liver cancer? Can HCV treatment have favorable effects on major concomitant disorders such as diabetes or cardiovascular disease? Is there any cause for concern when using DAAs in HCV patients with a concomitant hepatitis B virus (HBV) infection?

WHAT BENEFITS CAN BE EXPECTED FROM ERADICATING HCV IN PATIENTS WHO ALREADY HAVE ADVANCED LIVER DISEASE?

The new-generation DAA regimens sofosbuvir/velpatasvir and glecaprevir/pibrentasvir have shown rates of SVR higher than 95% in patients with cirrhosis, independent of genotype. No concerns about their safety have been described[2,5,8]. Notably, these results have been confirmed in real-world studies conducted in large and heterogeneous populations, including patients with intravenous drug use, patients with advanced chronic kidney disease or those aged over 70, who are usually excluded from registrational trials[9,10].

Previous studies demonstrated the favorable effects of viral eradication on the histopathological features of cirrhosis, showing that SVR is associated with a histological decrease in fibrosis or cirrhosis regression[11]. More recently, various studies have shown the clinical advantages of treating HCV infection in patients with cirrhosis. One study analyzed a large French cohort of 1323 patients with biopsy-proven cirrhosis, showing that SVR was significantly associated with reductions in the risk of decompensation and of both overall and liver-related mortality[12]. The association between SVR and reduction in mortality for all causes was confirmed by another French study including 9895 cirrhotic patients followed up for more than 33 mo[6].

Another large cohort study from the United States evaluated the impact of DAA-induced SVR on all-cause mortality in 15059 HCV patients with advanced liver disease. SVR was independently associated with a reduced risk of death compared to no SVR (hazard ratio: 0.26; 95% confidence interval: 0.22-0.31; $P < 0.001$)[13].

Studies on hemodynamics have examined the relationship between SVR and portal hypertension. A reduction in the hepatic venous pressure gradient (HVPG) has been reported after SVR with DAA, leading to a reduced risk of hepatic decompensation[14].

Are such relevant results confirmed when patients with more advanced/decompensated cirrhosis are considered?

DAAs have been used in patients with Child-Pugh B and C cirrhosis who were unsuitable for treatment with IFN-based regimens. Although such patients remain harder to treat and protease inhibitors are contraindicated in this setting, various studies have reported SVR rates higher than 90% after adding ribavirin or prolonging treatment to 24 wk[15-17].

Even in patients with advanced cirrhosis, virological response is associated with a clinical benefit. Model for end-stage liver disease score and liver function improve in one third to one half of treated patients. Furthermore, treatment is well tolerated with no safety concerns[18].

Hepatic venous pressure gradient reduction after SVR has been observed even in Child-Pugh class B cirrhosis[19], but the benefits for portal pressure can be reduced in patients with more advanced liver cirrhosis. In a multicenter prospective study, although a significant reduction in hepatic vein pressure gradient was observed after SVR, this reduction was only marginal in patients who had higher, clinically significant portal hypertension at baseline[20].

Strong evidence of the clinical impact of DAAs in these patients can be found in the setting of OLT. HCV-related liver disease has been the most common indication for OLT in Western Europe for the last 20 years. DAA introduction has significantly contributed to change the OLT scenario, greatly decreasing the burden of HCV disease at waiting list registration. Data from an Italian cohort showed that after the extended approval of DAA therapies was granted in Italy in 2014, waiting list registrations for OLT due to HCV-related disease decreased from 43.3% of all waiting list registrations in the pre-DAA period to 37.2%[21].

Data from the European liver transplantation cohort showed that treatment with DAAs allowed as many as one third of patients already on waiting list to be delisted because of clinical improvement, with a very low risk of a subsequent need for relisting[22].

High rates of SVR have also been demonstrated in patients treated after transplantation[23]. A study from Spain conducted in 112 OLT recipients showed SVR to be associated with liver fibrosis regression and a significant improvement in liver function and survival[7].

In conclusion, DAA treatment allows high rates of SVR even in patients with advanced cirrhosis. These patients remain difficult to treat, are not suitable for protease inhibitors and may require treatment prolongation and ribavirin use. SVR is associated with an improvement in liver function and a reduction in portal pressure in a large proportion of patients. DAA availability has reduced the burden of HCV-

related disease in the liver transplantation setting (Table 1).

IS DAA-INDUCED SVR ASSOCIATED WITH AN APPRECIABLE BENEFIT IN HCC?

A number of studies have evaluated the role of DAA-induced SVR in both the occurrence and recurrence of HCC. Overall, SVR obtained with DAAs is associated with a 70% incidence reduction[24].

A retrospective cohort study on a large population from the United States evaluated the annual rates of HCC in HCV patients treated with DAA, comparing those who achieved SVR to those who did not. The study included 22500 patients treated with DAA; about one third of them had cirrhosis. SVR was achieved in 19518 but not in 2982. The highest risk of HCC was reported in cirrhotic patients. Even though SVR significantly reduced the risk of HCC, the absolute risk of HCC remained high in patients with cirrhosis despite SVR. Thus, patients with cirrhosis should be kept under long-term surveillance for HCC[25].

Another real-world study from Italy, including a cohort of more than 2000 cirrhotic patients, showed a significant reduction in HCC risk after achieving SVR in patients with Child-Pugh class A and class B disease. Nevertheless, the mean time lapse between exposure to DAAs and HCC occurrence was 9.8 mo, with no significant difference between patients with SVR and those without; this observation would suggest that the high incidence of HCC described in the first year after DAA might be largely related to the presence of previously unrecognized HCC cases. Thus, previously unrecognized HCC could largely contribute to an overestimation of the early risk of HCC after DAAs[24,26]. In this study, albumin levels and platelet counts, associated with liver function and portal hypertension, respectively, were identified as significant predictors of HCC occurrence.

More recently, similar results have been confirmed in long-term follow-up studies. A retrospective study from East Asia, involving a large cohort of 5814 HCV patients treated with DAA and followed up for a median of 2.9 years, reported a significant reduction in HCC risk in SVR patients compared with those without SVR[27].

Another retrospective study was recently conducted in 129 Veterans Health Administration hospitals. Results confirmed that in cirrhotic patients successfully treated with DAA, the occurrence of HCC was reduced but remained high enough to warrant long-term HCC surveillance. Interestingly, the risk of HCC remained stable over the 3 year observation period[28].

Several studies have evaluated the risk of HCC recurrence in DAA-treated HCV patients on HCC remission at DAA initiation. Some early studies raised concerns about an increased risk of HCC recurrence in patients treated with DAAs compared with those receiving IFN. Furthermore, other studies hypothesized that the rapid clearance of HCV during DAAs could decrease the immune surveillance of small HCC clones, increasing the risk of early HCC recurrence[29].

A meta-analysis published in 2017 compared the risk of HCC recurrence in patients treated with DAA or IFN-based treatments, finding no difference between the two groups. In particular, DAA treatment was not associated with a higher HCC recurrence[30]. More recently, a retrospective, population-based cohort study including 17836 patients confirmed that neither the HCC incidence rate nor HCC-free survival were significantly different in the DAA group compared to the IFN group[31].

A large retrospective cohort study from the United States and Canada found no significant differences in either overall or early HCC recurrence between patients who received DAAs and patients not receiving therapy after a complete response to HCC treatment[32]. Even if the risk of HCC recurrence appears not to be affected by curative DAA treatment, a reduction in the risk of decompensation of cirrhosis has been observed in these patients, and overall survival appears to be improved in those achieving SVR[33].

A retrospective cohort study from the United States and Canada, including 797 patients with previous HCV-related HCC who had achieved a complete HCC response at treatment initiation, confirmed that SVR after DAA treatment was associated with a significant reduction in the overall risk of death[34]. A history of previous HCC recurrence and previous main tumor size appear to be related with the risk of recurrence[35].

In conclusion, the available data show that HCC incidence is reduced in DAA-treated patients. The risk of HCC recurrence appears unaffected, but overall survival can be increased in these patients because of the reduced risk of decompensation. The

Table 1 Benefits and pitfalls of sustained virological response using direct-acting antivirals in different hepatitis C virus scenarios

Setting	Benefits	Pitfalls
Advanced liver disease	SVR rates higher than 95%; Reduced risk of decompensation and deathHVPG reduction	Nothing to report
Decompensated cirrhosis	Liver function improvement in one third to one half of patients; Treatment well-tolerated	Slightly lower SVR rates; Need for ribavirin or treatment elongation to 24 wk
HCC occurrence	Reduced occurrence of HCC	Still relevant risk of HCC; Need for periodic surveillance for early diagnosis
HCC recurrence	Improved survival due to reduced risk of decompensation	Risk of HCC recurrence unaffected by SVR; Need for periodic surveillance for early diagnosis
Diabetes	Reduced incidence of diabetes; Improvement of glycemic control	Risk of hypoglycemia in patients receiving antidiabetic medications; Adjustments of antidiabetic medication may be necessary
Cardiovascular diseases	Decreased risk of cardiovascular events; Reduction in cardiovascular deaths	Nothing to report
HBV coinfection	As for general HCV population	Risk for HBV reactivation; Pre-DAA screening for HBV indicated; Need for HBV treatment or on-treatment HBV monitoring as requested

DAA: Direct-acting antiviral; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HVPG: Hepatic venous pressure gradient; SVR: Sustained virological response.

risk of both the incidence and recurrence of DAA remains high enough to warrant long-term surveillance after treatment, even in patients with SVR (Table 1).

CAN HCV TREATMENT HAVE FAVORABLE EFFECTS ON MAJOR CONCOMITANT DISORDERS SUCH AS DIABETES OR CARDIOVASCULAR DISEASE?

An interesting, albeit unsolved issue regarding the association between HCV infection and glucose abnormalities [insulin resistance (IR) and type 2 diabetes mellitus (T2DM)]. Even though the mechanisms that lead to the development of IR and T2DM in predisposed HCV-infected patients are not fully understood, HCV seems to play a direct role by interfering with glucose metabolism. As indicated by many studies, HCV-infected subjects have a significantly higher risk of T2DM than noninfected controls[36,37], HCV-cleared patients[38] and HBV-infected patients[39]. Moreover, some data suggest that the higher risk might be independent of body mass index and family history[40], strengthening the hypothesis of HCV as a direct cause of T2DM.

Although it is quite clear that HCV infection increases the risk of developing T2DM, the data regarding whether the stage of liver disease could affect the development of T2DM are ambiguous. Indeed, some studies show that HCV-related cirrhosis (and in particular decompensated cirrhosis) is associated with a higher risk of DM than in non-HCV cirrhosis, HCV-cleared patients and chronic HCV-infections[38]. Due to this close association between HCV infection and the development of T2DM, many studies have evaluated whether glucose abnormalities could on the contrary affect the natural course of HCV infection.

To our knowledge, DM and IR are associated with a worse outcome in patients with chronic hepatitis C, with an increased risk of developing liver cirrhosis and decompensation over time[41]. In particular, the effects of fasting glucose levels seem to be increased in genotype 1 and genotype 2 patients[42].

In a cohort study, baseline diabetes was independently associated with a higher prevalence of ascites, bacterial infections and encephalopathy detected at inclusion and was independently associated with the development of ascites, renal dysfunction, bacterial infections and HCC during follow-up, showing T2DM as an independent prognostic factor in patients with chronic hepatitis C and cirrhosis. Transplantation-free survival was also shortened, independent of the baseline model for end-stage liver disease score[43]. Furthermore, some data suggest an important role for new-onset diabetes in chronic hepatitis C patients, which seems to lead to a significantly higher cumulative incidence of HCC[37,44].

The effects of HCV eradication on glycometabolic control have been widely investigated. Although SVR after IFN/ribavirin therapies was already known to be

associated with a significantly reduced risk of developing T2DM after long-term follow-up[45-48], data collected in the DAA era suggest a great benefit of antiviral treatment in HCV patients who already have glucose abnormalities. Many studies have shown a significant improvement in insulin sensitivity[49], hemoglobin A1c and fasting glucose plasma levels in patients who achieved SVR after DAA therapy[50-53]. A prospective case-control study showed IR improvements in 76.5% of patients who achieved SVR and a normalized IR in about 41% of them, with these data being confirmed 3 mo after treatment withdrawal[54]. Moreover, patients with SVR also required a lower dose of antidiabetic medications than those without[51]. Interestingly, these metabolic changes seem to be body mass index-independent[55]. Nevertheless, more studies are needed to clarify the long-term effects after DAA therapy.

All these observations lead to another question: Does HCV eradication affect diabetes mellitus-related long-term complications? The clinical impact of successful antiviral therapy on the long-term outcomes of T2DM in HCV patients remains largely unknown, mainly because of the lack of specific prospective studies. However, based on the above-mentioned data, it is reasonable to presume that HCV eradication could also reduce long-term metabolic-related complications. A Taiwanese population-based cohort study found that better renal and cardiovascular outcomes were obtained in the group treated with the antiviral IFN/ribavirin regimen than in the untreated cohort[56]. Another study showed a decreased incidence of acute coronary syndrome, end-stage renal disease, ischemic stroke and retinopathy after HCV eradication, both with IFN and with DAA treatment, regardless of cirrhosis[57]. Whether the reduction in cardiovascular events observed in diabetic patients after HCV eradication is due to a beneficial effect on T2DM itself or to the disappearance of systemic chronic inflammation remains to be clarified.

Although HCV eradication has important benefits for glycometabolic control, some negative aspects of DAA treatment in diabetic patients must be considered. In fact, a Health Canada review has pointed out a link between DAA use and the risk of dysglycemia (including hypo/hyperglycemia and new-onset diabetes). The evidence was stronger concerning the risk of hypoglycemia in patients with an increased insulin sensitivity and a decreased need for antidiabetic medications[58]. Thus, patients with diabetes who start an anti-HCV therapy with DAAs should be closely monitored for changes in glucose levels, particularly in the first 3 mo of treatment, and adjustments to their diabetic medication or doses may be necessary.

Independent of the association between HCV and diabetes and diabetes-related consequences, HCV infection seems to be directly associated with an increased risk of cardiovascular disease. Emerging data show that HCV infection might increase the risk of cardiovascular disease by 20%[59]. HCV RNA has been found in the carotid plaques of infected subjects[60]. Thus, HCV could cause atherosclerosis through colonization and replication within the arterial wall[61], but other mechanisms may be involved, such as oxidative stress and the imbalanced secretion of inflammatory molecules[62-65], including C-reactive protein, soluble adhesion molecules and soluble E-selectin[66].

Does SVR have a favorable impact on major adverse cardiovascular events? It has been demonstrated that HCV clearance improves carotid atherosclerosis. Indeed, an intima-media thickness ≥ 1 mm has been associated with a higher risk of cardiovascular events[67,68], but when evaluated at 9-12 mo after the end of DAA-therapy, intima-media thickness and carotid thickening appeared significantly decreased compared to baseline.

An analysis of a large cohort of HCV-infected veterans evaluated the impact of HCV treatment on cardiovascular events in a population free of any cardiovascular disease at baseline. The study included 4436 patients treated with a pegylated interferon–ribavirin regimen, 12667 patients treated with a DAA regimen and 17103 HCV-infected matched controls. Results showed that HCV treatment both with IFN-based regimens and with DAAs was associated with a significantly decreased incidence of all cardiovascular events: Acute myocardial infarction, unstable angina, congestive heart failure, peripheral vascular disease, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting and stroke. The greatest benefits were observed in the DAA-treated group. Patients with advanced liver fibrosis at baseline had a higher incidence of cardiovascular events than those with minimal or no fibrosis. Nevertheless, a marked reduction in cardiovascular disease incidence was observed in treated patients independently of the degree of liver fibrosis, and patients with more advanced fibrosis received the greatest advantage[69].

A reduction in cardiovascular deaths after viral eradication has been observed in cirrhotic patients[70]. Moreover, a recent evaluation of the Italian Rete Sicilia Selezione Terapia-HCV cohort confirmed that DAA-induced SVR is independently associated with a reduction in the risk of both hepatic and cardiovascular mortality[71,72]. This observation has been further confirmed in other studies[73].

In conclusion, DAA treatment in HCV patients with glucose abnormalities is associated with an improvement in glucose control and a reduced need for antidiabetic medications. Furthermore, HCV eradication in diabetic patients seems to reduce the incidence of long-term vascular complications. However, glucose levels in HCV diabetic patients undergoing DAA treatment should be closely monitored because of the risk of hypoglycemia, and diabetic medications may need some adjustment.

DAA treatment is associated with a significantly decreased incidence of all cardiovascular events independent of the degree of liver fibrosis and is also associated with a reduction in the risk of both hepatic and cardiovascular mortality (Table 1).

IS THERE ANY CAUSE FOR CONCERN WHEN USING DAAs IN HCV PATIENTS WITH A CONCOMITANT HBV INFECTION?

In patients with a HCV-HBV coinfection, HCV is usually the main driver of chronic inflammation and viral activity, while HBV DNA levels are generally low or undetectable[1]. In these patients, HBV flares have been described after HCV suppression both by IFN-based treatments and by DAAs[74,75].

In 2016, the Food and Drugs Administration issued an alert about the risk of HBV reactivation in patients treated with DAAs. Notably, in some cases HBV reactivation resulted in severe liver disorders or death. The full data were subsequently published. They referred to 29 cases of HBV reactivation in HCV-HBV patients after treatment with DAAs. The median time lapse between DAA initiation and HBV reactivation was 46 d. Before DAA initiation, 13 patients were hepatitis B surface antigen (HBsAg) positive, 4 patients were HBsAg negative, and 12 patients did not have HBsAg reported. Two cases resulted in death and one case in liver transplantation[76,77].

Since then, various reports have been published on HBV reactivation in HCV-HBV patients treated with DAAs, both in HBsAg positive and in HBsAg negative/anti-hepatitis B core (HBc) positive patients[75,78,79]. The risk of HBV reactivation is lower in HBsAg negative/anti-HBc positive than in HBsAg-positive patients. An asymptomatic increase in HBV DNA level is generally observed, although clinically relevant events are infrequent[80].

On the basis of all these data, the European Association for the Study of the Liver guidelines state that patients undergoing DAA treatment for hepatitis C should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies. If HBsAg is present, then therapy with anti-HBV nucleoside/nucleotide analogue is indicated. In HBsAg negative/anti-HBc positive patients, monitoring for alanine transaminase levels, HBsAg and HBV DNA would be warranted during and after anti-HCV therapy[1].

In conclusion, in patients with HCV/HBV coinfection there is a risk of HBV reactivation after HCV clearance. However, the risk is low, particularly in HBsAg-negative/anti-HBc-positive patients. It is generally associated with an asymptomatic increase in HBV DNA levels, but threatening clinical events have been described. Patients undergoing DAA treatment should be tested for HBV infection (Table 1).

CONCLUSION

DAAs are extremely effective in eradicating infection. Furthermore, treatments are very well-tolerated, and their duration is reduced. Most of the information has been obtained from studies including patients with chronic hepatitis or early cirrhosis, whereas large studies in patients with advanced cirrhosis have shown slightly lower but still quite satisfactory response rates, although modified treatment schedules may be necessary.

Despite these enthusiastic results, some important points must be kept in mind. First, although the incidence of liver cancer is reduced after viral eradication, it remains high enough to warrant the continuation of periodic surveillance for an early diagnosis. The risk of recurrence seems to be unaffected, even if survival improves in treated patients because of the reduced risk of liver disease progression.

Furthermore, HCV eradication is associated with a reduced diabetes incidence and improved glycemic control, but there are concerns about the risk of hypoglycemia after virus clearance.

In patients with HCV/HBV coinfection, HBV reactivation after HCV clearance has been described, sometimes associated with clinically relevant events. Baseline evaluation for HBV coinfection is therefore mandatory before treatment.

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