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REVIEW

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The art of managing hepatitis C virus in special population groups: a paradigm shift

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Abstract

The first direct-acting antiviral (DAA) medications were approved for the treatment of chronic hepatitis C virus (HCV) in 2011. Later, the appearance of novel DAAs had revolutionized the landscape of HCV treatment whose early treatment options were limited to interferon (IFN) either alone or in combinations. This review discusses the paradigm shift in legibility for treating different groups of patients with HCV after the introduction of DAAs, along with the consequent changes in treatment guidelines. IFN-based therapy was the firstly used for treating chronic HCV. Unfortunately, it exhibited many pitfalls, such as low efficacy in some patients and unsuitability for usage in lots of patients with some specific conditions, which could be comorbidities such as autoimmune thyroiditis, or liver related as in decompensated cirrhosis. Furthermore, IFN failed to treat all the extrahepatic manifestations of HCV. Nowadays, the breakthroughs brought by DAAs have benefited the patients and enabled the treatment of those who could not be treated or did not usually respond well to IFN. DAAs achieve a high success rate of HCV eradication in addition to avoiding unfavorable harms and, sometimes, adverse effects related to the previously used PEGylated IFN regimens.

Keywords: Hepatitis C virus, Hepatitis C comorbidities, Extrahepatic manifestation, Special population, Direct-acting antiviral

Introduction

Hepatitis C virus infection is expected to affect roughly 130–150 million people worldwide [1]. HCV infection is one of the most common causes of chronic liver disease (CLD) globally. CLD spectrum includes chronic hepatitis and cirrhosis which comprise compensated and decompensated cirrhosis ending with hepatocellular carcinoma (HCC). A common indication of liver transplantation (LT) is HCV-related liver disease. Furthermore, 40–74% of HCV infected patients may experience at least one extrahepatic symptom during the course of the disease [2].

Since the 1990s and for the following 20 years, the standard anti-HCV therapy was the administration of interferon (IFN)-based agents, with various restrictions and high failure rates limiting their use in many patients [3, 4].

Many patients with HCV were ineligible for IFN therapy because of the coexistence of contraindications. PEGylated IFN/ribavirin (RBV) regimen was contraindicated in many neuropsychiatric conditions and it may cause severe adverse effects in patients with chronic diseases, such as cardiovascular diseases and autoimmune diseases, in addition to the parenteral route that being a limitation of IFN along with the injection-related adverse effects. Therefore, it was estimated that around 20% of patients with HCV were not able to receive IFN, which left a big burden of untreated patients [5].

The development of direct-acting antivirals (DAAs), which directly attack the viral replicative cycle at several points, had revolutionized the treatment of chronic HCV. These drugs have achieved a sustained virological response (SVR) of more than 95% [6]. These medications

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show a high safety profile and are administered for short periods. These factors allowed the treatment of special patient population, which were previously known to be difficult to treat [7]. In this review, we will discuss the paradigm shift in legibility for treating different groups of patients with HCV after the introduction of DAAs and the consequent changes in treatment guidelines.

Patients with HCV in special situations

Acute HCV

In the period of IFN-based therapy, treatment of individuals with acute HCV infection had a good outcome with a high SVR, and studies with PEG-IFN alpha-2b alone in intent-to-treat analyses found SVRs of 71–96% [3, 8, 9]. A meta-analysis of 22 studies with1057 patients using INF-based monotherapy for acute HCV showed an overall SVR rate of 78% [8]. The SVRs observed with IFN-based therapy of acute HCV are significantly higher than the SVRs observed with IFN or PEG-IFN-based treatment of chronic HCV. So, it was recommended to treat patients in the acute settings particularly within 12 weeks following diagnosis [9, 10].

The treatment of patients with acute HCV infection in the new era of DAAs therapy showed improvement in clinical outcomes and high cost-effectiveness as compared with the earlier practice of postponing therapy until the infection chronic phase [11]. In individuals infected with genotype 1 with varying SVRs, three clinical studies with sofosbuvir (SOF)/ledipasvir (fixed-dose combination) were conducted. After 4 weeks of treatment, SVRs in intravenous drug users were 93 % [12], after 6 weeks 77% in HIV coinfected individuals [13], and 100% in HIV-negative, non-injection drug users after 6 weeks [14].

The combination of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir administered for eight weeks had shown a SVR rate of 97% (29/30) in acute HCV infected patients in TARGET-3D study [15]. Based on these trials, the European Association for the Study of the Liver (EASL) in its latest guidelines in 2018 stated that patients with acute HCV infection should be treated with DAAs combinations for 8 weeks [16].

On the other side, the American Association for the Study of Liver Disease (AASLD) in its latest guidelines in 2019 affirmed that there are insufficient evidence for patients with acute HCV to support a specific treatment regimen or duration, hence treatment as stated is recommended until more conclusive data become available [17].

Chronic HCV with decompensated cirrhosis

The treatment of patients with HCV and decompensated cirrhosis in the era of IFN-based therapy was very difficult with low SVRs and primarily unsafe with many complications such as severe anemia, thrombocytopenia, bacterial sepsis, and the deterioration of liver functions. Because of this, it was not recommended to treat these groups of patients with IFN-based regimens and to defer their treatment after LT [18].

Recently, AASLD-Infectious Disease Society of America (IDSA) 2019 guidelines based on many randomized controlled trials have recommended the treatment of patients with decompensated cirrhosis under the supervision of an expert medical practitioner. Ideally, this process should be conducted in an LT center with many different options of DAAs regimens based on the HCV genotype, tolerability to RBV, and previous experience to antiviral drugs. It was proven that DAAs apart from protease inhibitors were safe and effective in these group of patients [17].

- Patient with decompensated cirrhosis: only genotype 1, 4, 5, or 6 only: daily fixed-dosage combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated to weight-based dose) for 12 weeks is a recommended regimen -Genotypes 1–6: daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks is also a recommended regimen.
- In patients who cannot tolerate or ineligible for ribavirin, extending the treatment up to 24 weeks is recommended.
- In patients with prior sofosbuvir-based treatment failure: genotype 1, 4, 5, or 6 only: daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg; increase as tolerated) for 24 weeks is a recommended regimen–genotypes 1–6: daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 24 weeks is also a preferred regimen [17].

HCV with coinfection

Chronic HBV

The cornerstone in the management of HCV/HBV coinfection is to determine, which is the common viral infection that must be primarily eliminated. A careful follow-up of viremia through the measurement of serum HBV DNA and HCV RNA levels is essential before the diagnosis of the viral dominance [19]. The therapy options for coinfected patients will be influenced by these viral interactions.

Subsequently, Liu et al. carried out a multicenter study using PEG-IFN and RBV in patients coinfected with

HCV/HBV. Such regimen is equally proven effective in patients with HCV alone or chronic HCV/HBV coinfection [20].

Patients prepared to receive DAAs for chronic HCV should be tested for hepatitis B surface antigen (HBsAg), anti-hepatitis core antibodies (anti-HBc), and anti-HBs antibodies. If HBsAg is present, then the concomitant administration of HBV nucleoside/nucleotide analog is recommended. In antigen-negative HBs, anti-HBc antibody-positive patients, the serum alanine transaminase (ALT) levels must be monitored. Additionally, both HBsAg and HBV DNA should be tested if ALT levels fail to normalize or rise during or after anti-HCV therapy. The follow-up of serum ALT levels is preferred in anti-HBs and anti-HBc antibody-positive patients [21].

In a cohort of HBsAg-positive Egyptians with chronic HCV infection treated with DAAs, the risk of HBV reactivation was 28.6% (95%CI 15.6–46.4%) and the risk of hepatitis was 10.0% (0.9–57.8%) in those who experienced reactivation in the absence of concomitant HBV treatment. Additionally, this systematic analysis included the Egyptian data, which showed that the pooled reactivation risk in HBsAg-positive individuals was 18.2% (95%CI 7.9–30.7%) and the risk of hepatitis in those who had reactivation was 12.6% (95%CI 0.0–34.7%). Among this investigation, the pooled reactivation risk in HBsAg-negative anti-HBc-positive patients was low regardless of the presence of anti-HBs [22].

Chronic HIV

Until 2011, the combination therapy of PEG-IFN+ RBV, despite being the therapy of choice for chronic HCV, it is rarely used in patients with HIV or HCV coinfection due to its low efficacy and high rate of significant adverse effects in these patients. In the APRICOT study, patients with HCV/HIV coinfection were treated with PEG-IFN α-2a and a fixed-dose of RBV (800 mg/day) for 48 weeks, and only 40% of patients achieved SVR [23].

After the introduction of DAAs, patients with HCV/HIV coinfection treated with DAAs HCV regimens can obtain SVR at the rates comparable to patients not infected with HCV [24–26]. In 2015, Naggie et al., conducted a study that included 335 patients with HCV/HIV coinfection and found that overall of 322 patients (96%) had achieved a sustained virological response 12 weeks after the end of treatment [27].

The switch between various antiretroviral drugs can be done to make DAA compatibility possible and to both treat HCV infection and maintain HIV suppression without compromising future events. The factors that need to be considered are previous treatment history, antiretroviral treatment response(s), resistance profiles, and medication tolerance [28].

An important issue in such special situation is that both regimens must be cognizant of drug–drug interactions to minimize negative effects and reduced efficacy. Many HIV antiretroviral (ARV) medicines, such as efavirenz, etravirine, and nevirapine, are not suggested to be used with DAAs (e.g., simeprevir, following fixed combination VEL/SOF, 3D, and EBR/GZR). Many antiretroviral medications used to treat HCV/HIV coinfections can be safely used with sofosbuvir and the fixed combination LDV/SOF [29].

HCV resistance to DAAs

Despite the high SVR implemented using DAAs, the emergence of hepatitis C resistant variants, resulting from mutations due to amino acid substitutions in the viral target protein, remains challenging [30]. Drug-resistant variants of hepatitis C exist naturally prior contact to DAAs. Hepatitis C virus (HCV) attains high replication capacity, which is estimated by ability of production and clearance of 10 10–1012 virions/day and has a short virion half-life of just 2–3 h together with probable errors in the replication mechanism, predisposing to the constant emergence of a great number of genetically diverse variants that can be resistant to DAAs [31].

Resistance-associated variants (RAVs) are usually detected in patients' experienced virological breakthrough. Meanwhile, they can vary from 53 to 91% in patients with viral recurrence according to the treatment regimen, the DAA used, and the duration of treatment [32]. Clinically, short-term or ribavirin-free regimens and poor adherence to treatment are risk factors for failure of DAAs therapy [30]. In conclusion, using combination of antiviral drugs with different mechanisms of action, high genetic barrier to resistance, and without cross resistance are the most effective method for preventing the emergence of resistant variations [30].

HCV recurrence after liver transplantation (LT)

Treatment strategies for patients with HCV who underwent LT were put on the waiting list to clear the virus before LT to prevent the recurrent infection of the graft after LT. Alternatively, the more commonly used strategy that was to treat patients after LT who already had progressive or severe liver disease, hence aiming to achieve the required SVR that was difficult to accomplish with a dual therapy of PEG-IFN and RBV in both situations because of a long duration of therapy, poor tolerability, and low efficacy [33].

Previously, the IFN-based antiviral therapy was the standard of care; this treatment showed higher serum viral response rates at 12, 24, 48, and 72 weeks after the initiation of treatment. Additionally, PEG-IFN plus RBV

was more effective than PEG-IFN alone following OLT [34].

Post-transplant treatment of HCV recurrence is currently centered on DAA agents; however, treatment should be attempted only at centers with considerable experience in the management of post-OLT patients. Because of the significant drug–drug interactions with paritaprevir/ritonavir/ombitasvir and dasabuvir regimen and calcineurin inhibitors (cyclosporine and tacrolimus) requiring dose reduction of the calcineurin inhibitor and frequent monitoring, this regimen is reserved for patients with genotype 1 recurrent HCV who need an alternative to a fixed-dose of SOF and ledipasvir along with RBV [35, 36]. Treatment with DAAs offers a new hope for a large category of patients, as they improve the outcomes and decrease the chances of recurrence.

HCV in pregnant and lactating women

The prevalence of HCV among pregnant women ranged from 0.1 to 8% in different countries and settings [37, 38]. Before the appearance of DAAs, the two cornerstones of treatment were the IFN and RBV that showed teratogenic and abortifacient side effects, which prevent their use in the setting of pregnant and breastfeeding patients [39]. After the appearance of DAAs, the treatment of these groups of patients were not recommended as there were no large-scale clinical trials assessing the safety of DAAs during pregnancy.

HCV in children

In the past, IFN-based regimens gave limited success rates either in adults or children with genotype 1 or 4 infections. IFN and RBV, in general, have specific toxic effect on children (growth impairment) that are not reported with DAA regimens [40].

Recently, DAA regimens are available for adolescents who are 12 years and older. SVR was achieved by 98% of patients in a multicenter open-label study of 100 adolescents with persistent genotype 1 infection treated for 12 weeks with the adult formulation of ledipasvir–SOF. In this population, the treatment regimen was safe and well-tolerated, and the adult dose formulation produced pharmacokinetic findings similar to those seen in adults [40].

Once daily dose of sofosbuvir/velpatasvir for 12 weeks was studied for treatment of 173 pediatric patients aged $\geq$ 6 years with various genotypes, and in presence or absence of cirrhosis, an overall SVR12 of $\geq$ 92% was achieved across genotypes [41]. This combination was approved by the FDA for children aged $\geq$ 6 years in March 2020. Being pangenotypic, safe, and effective, sofosbuvir/velpatasvir becomes the first choice for HCV treatment in pediatric at least 6 years of age [35].

HCV patients with tumors

HCC

During the era of IFN in the treatment of HCV, many studies have found that SVR after IFN treatment had decreased the incidence of HCC with increased survival rates and reduced the recurrence risk of HCC after curative intervention [42]. The antitumor effect of IFN with direct immunostimulatory effect could lower the risk of HCC development after IFN treatment [43]. Following HCC ablation or resection, IFN has been demonstrated to enhance outcomes. Some studies have recommended the use of IFN after the curative intervention of HCC after 3–6 months of HCC treatment. This intervention could decrease the incidence and recurrence of new HCC following IFN treatment [44]. DAAs are seen as a crucial and difficult step in the management of HCC in this modern era. Antiviral medication should be started as soon as possible in individuals with HCC who are candidates for LT [45, 46]. Antiviral treatment can be started before transplantation to prevent infection recurrence, or it can be postponed until after transplantation, with a higher chance of achieving a high SVR [47]. The timing of starting DAAs after intervention also remains debated. However, there are some recommendations to wait for 6–12 months post-HCC interventions to start treatment with DAAs [48]. In contrast, multiple centers reported an increased the HCC recurrence risk following the treatment of HCV infection by DAAs regimen.

Others reported a reduction in the recurrence rate significantly as compared to untreated persons. Nevertheless, the data about HCC recurrence after DAAs treatment still present conflicting results [49].

Lymphoma

There is a strong association between HCV infection and some types of B cell non-Hodgkin lymphomas (NHL), mainly marginal zone lymphoma and aggressive diffuse large B cell lymphoma (DLBCL) [50].

Antiviral treatment is effective for low-grade lymphomas. Early studies used IFN-α, but later studies used PEGylated IFN with and without RBV for the treatment of specific types of HCV-related lymphomas with excellent results. An Italian study followed 704 HCV-positive patients with B-NHL between 1993 and 2009 at 39 centers. In total, 100 patients received either IFN-α or PEGylated IFN alone or with RBV as the first-line therapy. About 80% of patients achieved a clearance for HCV, whereas 44% and 33% achieved complete and partial remissions of B-NHL, respectively [51].

In the era of DAAs, many studies have demonstrated highly encouraging results regarding lymphoma regression after HCV clearance with DAAs. A recent

international multicenter study involving 46 patients with indolent NHL or chronic lymphocytic leukemia and HCV infection reported a higher efficacy of DAAs in that setting. Most patients (n=39) were treated with a SOF-based therapy, whereas seven patients received other regimens with an excellent safety profile. SVR was achieved in 98% of cases with lymphoproliferative disease response (LDR) in 67% of cases [52]. Concurrent DAAs and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone treatment resulted in a feasible outcome and may prevent the hepatic toxicity of immune-chemotherapy. Therefore, in indolent HCV-associated NHL, DAAs, therapy may achieve a high LDR rate and should be considered as the first-line therapy in patients without the need for urgent treatment. In DLBCL-associated HCV, the immediate delivery of DAAs may be recommended in patients achieving a complete response after first-line immunochemotherapy. However, in some cases, especially those with severe hepatic toxicity, the use of concurrent DAAs with immunochemotherapy may be adopted [53].

Other extrahepatic tumors

Studies of anti-HCV therapy typically exclude patients with cancer; therefore, the data available on HCV treatment in patients with cancer are limited. DAA therapy can be administered in patients with cancer alongside bone marrow suppression without dose adjustments or discontinuation, unlike IFN-based treatments. DAAs should be offered for patients with HCV and cancer unless there are contraindications such as uncontrolled cancer, a life expectancy of fewer than 12 months, anticipated major drug–drug interaction, and/or known hypersensitivity or intolerance to DAAs [54].

HCV in patients with comorbidities

Cardiovascular disease

HCV eradication have been proven to exhibit favorable cardiovascular outcomes by modifying the metabolic risk factors. However, when IFN was the only available treatment for HCV, many patients were ineligible for treatment because of cardiac side effects. Cardiovascular complications were reported in 18% of 194 Egyptian patients with chronic HCV without pre-existing cardiovascular disorders who were followed up for 6 months after being treated with PEGylated IFN/ribavirin, wherein the left ventricular dysfunction and reduced ejection fraction were the commonest adverse events [55].

Given that the high safety and efficacy of DAAs encourage that chronic HCV and cardiac comorbidity should be offered antiviral therapy expect those with a shorter life expectancy [56]. Although data are still inadequate to assess the real-life outcomes of DAAs treatment in those patients, a study reported a good safety profile of DAAs on the right and left ventricular functions [57].

DAAs treatment in patients with cardiac diseases requires special precautions to avoid drug–drug interactions with antiarrhythmic drugs and statins. For example, amiodarone is contraindicated if co-administered with SOF for the risk of bradycardia [56].

As a result, the emergence of DAAs has provided several advantages, such as short treatment duration, high safety profile, and high rate of SVR (> 90%), to patients. Additionally, DAAs were proved to be more efficient than PEGylated IFN and RBV in lowering the incidence rates of cardiovascular disease events [58, 59].

Renal diseases

The renal affection rests on the top of the list of extrahepatic HCV manifestations [60].

HCV-associated nephropathies

The commonest form of HCV-related nephropathy is membranoproliferative glomerulonephritis, which is commonly linked to essential mixed cryoglobulinemia [60]. When PEGylated IFN/RBV was the standard-of-care therapy, great problems had arisen because of the serious side effects of IFN and the low SVR rates. The advent of the new DAAs therapy has opened a new gate of hope for this difficult-to-treat group of patients as this treatment is very well-tolerated and associated with very high rates of viral clearance. IFN- and RBV-free DAAs regimens are recommended for the treatment of cryoglobulinemia, according to the recent guidelines. A careful monitoring of adverse events is mandatory [61].

HCV and kidney diseases

The incidence of HCV among patients with end stage kidney disease ranges from 6 to 50% in developing countries [62]. Patients with HCV and chronic kidney disease should be evaluated for DAAs therapy, and treatment should be tailored according to the viral genotype, the extent of liver disease, and the glomerular filtration rate [63]. Patients with mild to moderate renal dysfunction are treated according to the general recommendations without any dose modifications. In patients with severe renal dysfunction whose glomerular filtration rate is less than 30 ml/min, SOF-containing regimens are unsafe as its main route of excretion is via the kidneys; however, some studies recently demonstrate the safe use of small dose of sofosbuvir in patients with HCV-related severe renal dysfunction [64]. Different SOF-free regimens are recommended for this group of patients, for example ritonavir-boosted paritaprevir/dasabuvir/ombitasvir for

12 weeks , glecaprevir /pibrentasvir for 8–12 weeks or elbasvir/grazoprevir for 12 weeks [65].

HCV and renal transplantation

HCV infection is associated with significant morbidity and mortality in renal transplant recipients, which is attributed to its hepatic and extrahepatic complications [63]. The HCV-related hepatic injury may be increased by immunosuppressive therapy. Therefore, it is recommended to treat all the patients undergoing renal dialysis who are the candidates for renal transplantation to prevent graft dysfunction following interferon therapy; moreover, it was proven that HCV eradication prior transplant improves the post-transplant clinical outcomes. Following introduction of DAAs therapy, it became possible to treat HCV after renal transplantation taking in consideration drug–drug interactions in the post-transplant period [66].

In treatment-Naïve with or without compensated cirrhosis in all genotypes, it is recommended by the AASLD-IDSA HCV guidelines to give 12-week course of Sofosbuvir–velpatasvir, Sofosbuvir–ledipasvir, or glecaprevir–pibrentasvir; however, in treatment-experienced patients, a 12-week regimen of Sofosbuvir–voxilaprevir–velpatasvir with or without ribavirin is recommended [67].

Pulmonary diseases

Previously, PEGylated IFN and RBV combination was the only available treatment for HCV and its related complications; however, it was associated with the deleterious pulmonary side effects such as interstitial pneumonitis and consequently pulmonary hypertension; therefore, IFN-α was declared by the European Society of Cardiology (ESC) to be a probable cause of pulmonary hypertension. The effects of DAAs therapy on pulmonary hypertension are still unknown; however, some reports showed that DAAs therapy is neither associated with pulmonary hypertension nor with right ventricular dysfunction [68]. Moreover, alveolar lavage in patients who had completed DAAs therapy showed a marked reduction of the inflammatory activity [69].

There are not sufficient research addressing the effect of DAAs therapy on the pulmonary extrahepatic manifestations of HCV. Recently, in a study performed on a number of patients receiving sofosbuvir–simeprevir–ribavirin regimen, they noticed that some of these patients suffered from dyspnea and reported a single death owing to the presence of extensive alveolar damage [70].

HCV in patients with diabetes

Studies conducted during the era of IFN therapy for chronic HCV indicated a significant decline in fasting glucose and glycated hemoglobin (HbA1C) levels when patients obtained SVR. Patients with persistent HCV relapse did not experience this decline [71, 72]. IFN was previously used in the HCV infection treatment with a significant reduction of IR during the follow-up after achieving SVR, which subsequently led to a decrease in the frequency of DM in those patients [73].

In the era of DAAs, comparable improvements in glycemic indices were achieved [74]. Multiple studies revealed a reduction in the frequency of IR and DM after the administration of DAAs [58, 73]. It is still debatable if this good effect will last for a long period. To establish the permanence of such a link, large prospective cohort studies with an appropriate investigation of relevant confounding factors are still required.

Patients with extrahepatic manifestations of HCV

Neuropsychiatric manifestations

Chronic fatigue syndrome and depression are by far the most commonly encountered neuropsychiatric manifestations of HCV. They significantly affect the patient's quality of life. Furthermore, anti-HCV therapy is sometimes associated with side effects affecting the patient's quality of life and consequently, negative depressive feelings. This observation was evident in the era of IFN therapy as depression and suicidal attempts were very well-known side effects of IFN. Thus, it is recommended to check the patient's mental health before treatment initiation [75]. The novel DAAs have altered HCV treatment landscapes by ensuring higher success rates and by diminishing the deleterious adverse events related to PEGylated IFN regimens. Thus, it appears to be a promising and safe treatment option for patients with neuropsychiatric manifestations, yet, the effect of treatment differs according to the pattern of neurological involvement [75].

Immune-mediated extrahepatic manifestations

Apart from liver affection, chronic HCV infection is also responsible for many extrahepatic implications of variable etiology as shown of which a large proportion are immune-mediated [76]. In recent years, there has been a lot of interest in the link between systemic autoimmune disorders and chronic HCV infection. Sjogren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus are the most often reported diseases, accounting for about half of all cases in the Mediterranean basin [77]. The presence of antinuclear antibodies with rheumatoid factor and cryoglobulins were the most common immunological characteristics in patients with SAD and HCV infection [78]. For HCV-associated systemic autoimmune diseases, the SVR had no impact on the incidence. Additionally, there is no conclusive evidence that antivirals are beneficial to these people [79].

Patients with dermatological manifestations

Among the extrahepatic manifestations of chronic HCV, dermatologic manifestations, which significantly increase morbidity and the overall cost burden on the health care system, are most prevalent [79]. Dermatologic adverse events in HCV infection may result from the infection per se or may be related to the administered medications. Most, if not all, of the dermatologic manifestations, disappear after viral clearance. However, INF-based therapy was associated with dermatological complications. Real-world experience with INF-free DAA regimens reported decreased dermatological manifestations as compared to INF-based regimens [80].

Cryoglobulinemia is the most prevalent extrahepatic manifestations of HCV infection. Previously, the combined antiviral interferon/ribavirin therapy was considered the first-line together with plasmapheresis, immunosuppressive drugs, and/or rituximab in refractory cases [81].

In DAAs era, achieving SVR with triple therapy (interferon/ribavirin/first generation DAA) was associated with improvement in both clinical symptoms and serum cryoglobulin measurements [3, 82]. Further studies suggest that DAAs are effective therapy for cryoglobulinemia symptoms particularly with achievement of SVR and should be the first-line therapy of HCV-induced cryoglobulinemia, meanwhile plasmapheresis, immunesuppressive drugs, and/or rituximab could be saved for refractory patients [83].

Concerning HCV-associated mixed cryoglobulinemic vasculitis, IFN-based therapy was found to be the most effective when combined with rituximab. Though INF-free DAAs assure high SVR rates, the clinical data of their efficacy in patients with HCV-associated cryoglobulinemic vasculitis are disappointing, possibly because of their inability to suppress the immune-mediated process once it has been induced [84].

Lichen Planus (LP) is one of the first dermatological derangements associated with chronic HCV infection [85]. Psoriasis, another chronic inflammatory skin disease, has been stated in patients with HCV, especially with IFN-based HCV therapy [86]. However, the clinical outcomes of psoriasis symptoms has been promising after treatment with DAAs [87]. The most prevalent form of porphyria is porphyria cutanea tarda (PCT), which is caused by a decrease in the activity of uroporphyrinogen decarboxylase in hepatocytes [88]. The prevalence of HCV RNA positivity was reported as 50% among patients with PCT in an extensive systematic review [89]. Because RBV is known to produce hemolytic anemia, combined INF/RBV therapy may aggravate or generate PCT in predisposed patients, increasing hepatic iron overload and progressing to clinically evident PCT. DAAs-based HCV therapy, unlike INF/HBV HCV therapy, could be safe, effective, and not associated with the onset or worsening of PCT when associated with hepatitis C [90].

Summary

The treatment of acute HCV infection in the era of DAAs using DAA combinations offers a shorter duration of treatment, good tolerability and higher SVR than PEG-INF. In HBV/HCV coinfection, HCV treatment should be started by DAAs as soon as possible after a full-HBV assessment for the eligibility of treatment. In addition to a regular follow-up of the HBV was recommended after HCV eradication to immediately start treatment when indicated. Moreover, the rate of HCV SVR achieved by the DAAs therapy in patients with HCV/HIV was comparable to patients not infected with HCV. However, we should select the DAAs regimen and adjust the dose to avoid drug–drug interactions with antiretroviral drugs taken by each patient.

On the contrary of PEG-INF-based regimens, some DAA regimens (SOF/LED–SOF/REB) were proved to be safe and well-tolerated in adolescent aged 12–18 years with a high SVR rate; therefore, drugs will be available for children aged 3–11 years. Owing to the low tolerability and poor efficacy of PEG-INF/REB in patients with severe progressive liver diseases that listed for LT, HCV treatment for most patients was deferred to post-transplantation. DAAs treatment provides a new hope for this large category of patients, either by pretransplant HCV eradication to avoid post-transplant recurrence or even in the case of post-transplantation as it is effective and well-tolerated. Now, it is almost clear that the eradication of HCV by DAAs lowers the incidence of HCC, especially in high-risk patients with cirrhosis and post-HCV, who were difficult to be treated before and during the IFN era. However, its role in preventing or increasing HCC recurrence is still debatable and needs further research. Table 1 summarizes the differences in treatment decisions for some HCV special population groups between interferon era and after DAAs evolution.

The novel DAAs have altered HCV treatment landscapes by ensuring higher success rates and diminishing the injurious adverse events related to PEGylated IFN regimens in many special groups of patients such as those with extrahepatic manifestations of HCV. It also opened a new gate of hope for patients with concomitant comorbidities such as chronic kidney diseases either with or without dialysis. Also, patients with chronic HCV and cardiac comorbidity offers more compliance, higher SVR, and generally better outcomes than IFN-based therapy, but significant efforts should be made to avoid drug–drug interactions and conduct a close monitoring of such multi-medicated patients.

Table 1 Summary of the treatment difference of some special groups of patients during the interferon era and after DAAs evolution

	Patients' group	Treatment during interferon era	Treatment after DAAs evolution
1	Acute HCV	Recommended with reasonable cost-effective issue.	Recommended with more efficacy, better tolerability, and shorter duration.
2	Chronic HCV with decompensated cirrhosis	Not recommended	Recommended in special LT centers with close patients' monitoring.
3	Chronic HCV-HBV coinfection	Recommended with lower efficacy of HCV and higher probability of HBV reactivation	Recommended with higher efficacy of HCV and lower probability of HBV reactivation
4	Chronic HCV-HIV coinfection	Infrequently used with limited efficacy and high incidence of serious adverse events	Recommended with tailored regimen to avoid only drug–drug interaction
5	HCV in pregnant and lactating women	Contraindicated	Contraindicated
6	HCV in children	Contraindicated	Available for adolescent ($\geq$ 12 years old)
7	HCV recurrence after liver transplantation	Usually, intolerable with low efficacy	Recommended with better tolerability and high efficacy
8	HCV with hepatocellular carcinoma	Recommended, decreasing HCC incidence and recurrence	Recommended, decreasing HCC incidence but debates on their role in HCC recurrence
9	HCV with lymphoma	Recommended with good results	Recommended with better results
10	HCV with cardiovascular diseases	Could be recommended with close co-monitoring by Cardiologist	Recommended with better tolerability
11	HCV with renal diseases	Not recommended	Recommended with good tolerability and outcome
12	HCV with interstitial pulmonary diseases	Not recommended	Data insufficient
13	HCV with diabetes mellitus	Recommended with good outcome	Recommended with good outcome and better tolerability
14	Patients with extrahepatic neuropsychiatric manifestations of HCV	Not recommended	Recommended
15	Patients with extrahepatic immune-mediated manifestations of HCV	Not recommended	Recommended with better tolerability and outcome
16	Patients with extrahepatic dermatological manifestations of HCV	Not recommended	Recommended with better tolerability and outcome

However, patients with interstitial pulmonary fibrosis, it was declared by ESC that INF leads to pulmonary hypertension; however, it was not clear that DAAs may be associated with pulmonary hypertension. Thus, it seems to be a promising and safe treating option for patients with immune-mediated extrahepatic, neuropsychiatric as well as dermatological manifestations.

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References

1. Razavi H (2020) Global epidemiology of viral hepatitis. *Gastroenterol Clin North Am*. 49(2):179–189. https://doi.org/10.1016/j.gtc.2020.01.001
2. Gill K, Ghazinian H, Manch R, Gish R (2016) Hepatitis C virus as a systemic disease: reaching beyond the liver. *Hepatol Int*. 10(3):415–423. https://doi.org/10.1007/s12072-015-9684-3
3. Esmat G, El Kassas M, Hassany M, Gamil M, El Raziky M (2014) Optimizing treatment for HCV genotype 4: PEG-IFN alfa 2a vs. PEG-IFN alfa 2b; the

debate continues. *Liver Int*. 34(SUPPL1):24–28. https://doi.org/10.1111/liv.12397
4. Mayberry J, Lee WM (2019) The revolution in treatment of hepatitis C. *Med Clin North Am*. 103(1):43–55. https://doi.org/10.1016/j.mcna.2018.08.007
5. Talal AH, Lafleur J, Hoop RS et al (2013) Commentary: absolute and relative contraindications to pegylated-interferon or ribavirin in the US general patient population with chronic hepatitis C - Authors' reply. *Aliment Pharmacol Ther*. 38(5):554–555. https://doi.org/10.1111/apt.12424
6. Elbaz T, El-Kassas M, Esmat G (2015) New era for management of chronic hepatitis C virus using direct antiviral agents: A review. *J Adv Res*. 6(3):301–310. https://doi.org/10.1016/j.jare.2014.11.004
7. Suda G, Ogawa K, Morikawa K, Sakamoto N (2018) Treatment of hepatitis C in special populations. *J Gastroenterol*. 53(5):591–605. https://doi.org/10.1007/s00535-017-1427-x
8. Corey KE, Ross AS, Wurcel A et al (2006) Outcomes and treatment of acute hepatitis C virus infection in a United States population. *Clin Gastroenterol Hepatol*. 4(10):1278–1282. https://doi.org/10.1016/j.cgh.2006.06.026
9. Delwaide J, Bourgeois N, Gérard C et al (2004) Treatment of acute hepatitis C with interferon α-2b: Early initiation of treatment is the most effective predictive factor of sustained viral response. *Aliment Pharmacol Ther*. 20(1):15–22. https://doi.org/10.1111/j.1365-2036.2004.02023.x
10. Corey KE, Mendez-Navarro J, Gorospe EC, Zheng H, Chung RT (2010) Early treatment improves outcomes in acute hepatitis C virus infection: a meta-analysis. *J Viral Hepat*. 17(3):201–207. https://doi.org/10.1111/j.1365-2893.2009.01167.x
11. Bethea ED, Chen Q, Hur C, Chung RT, Chhatwal J (2018) Should we treat acute hepatitis C? A decision and cost-effectiveness analysis. *Hepatology*. 67(3):837–846. https://doi.org/10.1002/hep.29611
12. Lawitz E, Matusow G, DeJesus E et al (2016) Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: a phase 3 study (OPTIMIST-2). *Hepatology*. 64(2):360–369. https://doi.org/10.1002/hep.28422
13. Rockstroh JK, Bhagani S, Hyland RH et al (2017) Ledipasvir–sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. *Lancet Gastroenterol Hepatol*. 2(5):347–353. https://doi.org/10.1016/S2468-1253(17)30003-1
14. Deterding K, Spinner CD, Schott E et al (2017) Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. *Lancet Infect Dis*. 17(2):215–222. https://doi.org/10.1016/S1473-3099(16)30408-X
15. Martinello M, Bhagani S, Gane E et al (2018) Shortened therapy of eight weeks with paritaprevir/ritonavir/ombitasvir and dasabuvir is highly effective in people with recent HCV genotype 1 infection. *J Viral Hepat*. 25(10):1180–1188. https://doi.org/10.1111/jvh.12917
16. Pawlotsky J-M, Negro F, Aghemo A, et al. EASL recommendations on treatment of hepatitis C 2018 q. Published online 2018. doi:10.1016/j
17. AASLD-IDSA. (2019) Recommendations for testing, management, and treating hepatitis C. Unique populations: patients with decompensated cirrhosis. Published Accessed 9 Dec. 2020. https://www.hcvguidelines.org/unique-populations/decompensated-cirrhosis
18. Hézode C, Fontaine H, Dorival C et al (2013) Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol*. 59(3):434–441. https://doi.org/10.1016/j.jhep.2013.04.035
19. Raimondo G, Brunetto MR, Pontisso P et al (2006) Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfected patients. *Hepatology*. 43(1):100–107. https://doi.org/10.1002/hep.20944
20. Liu CJ, Chuang WL, Lee CM et al (2009) Peginterferon Alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology*. 136(2). https://doi.org/10.1053/j.gastro.2008.10.049
21. Lampertico P, Agarwal K, Berg T et al (2017) EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 67(2):370–398. https://doi.org/10.1016/j.jhep.2017.03.021
22. El Kassas M, Shimakawa Y, Ali-Eldin Z et al (2018) Risk of hepatitis B virus reactivation with direct-acting antivirals against hepatitis C virus: a cohort study from Egypt and meta-analysis of published data. *Liver Int*. 38(12):2159–2169. https://doi.org/10.1111/liv.13874
23. Torriani FJ, Rodriguez-Torres M, Rockstroh JK et al (2004) Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 351(5):438–450. https://doi.org/10.1056/nejmoa040842
24. Sogni P, Gilbert C, Lacombe K et al (2016) All-oral direct-acting antiviral regimens in hiv/hepatitis C virus-coinfected patients with cirrhosis are efficient and safe: real-life results from the prospective ANRS CO13-HEPAVIH cohort. *Clin Infect Dis*. 63(6):763–770. https://doi.org/10.1093/cid/ciw379
25. Department of Health and Human Services (DHHS). Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): A non-randomised, open-label trial. The Lancet HIV. doi:10.1016/S2352-3018(15)00114-9
26. Naggie S, Cooper C, Saag M et al (2015) Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. *N Engl J Med*. 373(8):705–713. https://doi.org/10.1056/nejmoa1501315
27. Naggie S, Cooper C, Saag M et al (2015) Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. *N Engl J Med*. 373(8):705–713. https://doi.org/10.1056/nejmoa1501315
28. Günthard HF, Aberg JA, Eron JJ et al (2014) Antiretroviral treatment of adult HIV infection: 2014 Recommendations of the International Antiviral Society-USA panel. *JAMA - J Am Med Assoc*. 312(4):410–425. https://doi.org/10.1001/jama.2014.8722
29. University of Liverpool. Liverpool HEP Drug Interactions Checker. Available from: https://www.covid19-druginteractions.org/checker. Last visited 13 March, 2022.
30. Buti M, Riveiro-Barciela M, Esteban R (2015) Management of direct-acting antiviral agent failures. *J Hepatol*. 63(6):1511–1522. https://doi.org/10.1016/j.jhep.2015.08.010
31. Rong L, Dahari H, Ribeiro RM, Perelson AS (2010) Rapid emergence of protease inhibitor resistance in hepatitis C virus. *Sci Transl Med*. 2(30). https://doi.org/10.1126/scitranslmed.3000544
32. Perales C, Quer J, Gregori J, Esteban J, Domingo E (2015) Resistance of hepatitis C virus to inhibitors: complexity and clinical implications. *Viruses*. 7(11):5746–5766. https://doi.org/10.3390/v7112902
33. Price JC, Terrault NA (2015) Treatment of hepatitis C in liver transplant patients: Interferon out, direct antiviral combos in. *Liver Transplant*. 21(4):423–434. https://doi.org/10.1002/lt.24080
34. Chen Y, Wu G, Zhang H, et al. Interferon treatment of hepatitis C reinfection after liver transplantation: a meta-analysis. *Gastroenterol Res Pract*. 2015;2015. doi:https://doi.org/10.1155/2015/206302
35. Ghany MG, Morgan TR. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology*. 2020;71(2):686-721. doi:https://doi.org/10.1002/hep.31060
36. Rammohan A (2021) Current management & future directions in post-liver transplant recurrence of viral hepatitis. *J Liver Transplant*. 3:100027. https://doi.org/10.1016/j.liver.2021.100027
37. Spera AM, Eldin TK, Tosone G, Orlando R (2016) Antiviral therapy for hepatitis C: Has anything changed for pregnant/lactating women? *World J Hepatol*. 8(12):557–565. https://doi.org/10.4254/wjh.v8.i12.557
38. Bigna JJ, Kenne AM, Hamroun A et al (2019) Gender development and hepatitis B and C infections among pregnant women in Africa: a systematic review and meta-analysis. *Infect Dis Poverty*. 8(1):16. https://doi.org/10.1186/s40249-019-0526-8
39. Prasad MR, Honegger JR (2013) Hepatitis C virus in pregnancy. *Am J Perinatol*. 30(2):149–159. https://doi.org/10.1055/s-0033-1334459
40. Balistreri WF, Murray KF, Rosenthal P et al (2017) The safety and effectiveness of ledipasvir—sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. *Hepatology*. 66(2):371–378. https://doi.org/10.1002/hep.28995
41. Jonas M, Romero R, Sokal E et al (2019) Safety and efficacy of sofosbuvir/velpatasvir in pediatric patients 6 to <18 years old with chronic hepatitis C infection [abstract 748]. *The Liver Meeting, Boston (USA)*
42. Tanimoto Y, Tashiro H, Aikata H et al (2012) Impact of pegylated interferon therapy on outcomes of patients with hepatitis C virus-related hepatocellular carcinoma after curative hepatic resection. *Ann Surg Oncol*. 19(2):418–425. https://doi.org/10.1245/s10434-011-1866-1

43. Ezzat WM, Amr KS, Elhosary YA et al (2019) Detection of DNA methylated microRNAs in hepatocellular carcinoma. *Gene*. 702:153–157. https://doi.org/10.1016/j.gene.2019.02.080
44. Jeong SC, Aikata H, Katamura Y et al (2007) Effects of a 24-week course of interferon-α therapy after curative treatment of hepatitis C virus-associated hepatocellular carcinoma. *World J Gastroenterol*. 13(40):5343–5350. https://doi.org/10.3748/wjg.v13.i40.5343
45. El Kassas M, Elbaz T, Salaheldin M, Abdelsalam L, Kaseb A, Esmat G (2019) Impact of treating chronic hepatitis C infection with direct-acting antivirals on the risk of hepatocellular carcinoma: the debate continues – a mini-review. *J Adv Res*. 17:43–48. https://doi.org/10.1016/j.jare.2019.03.001
46. Mazzarelli C, Cannon MD, Belli LS, Agarwal K (2018) Direct-acting antiviral therapy in patients with hepatocellular cancer: the timing of treatment is everything. *J Hepatol*. 68(1):217–218. https://doi.org/10.1016/j.jhep.2017.08.025
47. Pawlotsky JM, Negro F, Aghemo A et al (2018) EASL recommendations on treatment of hepatitis C 2018. *J Hepatol*. 69(2):461–511. https://doi.org/10.1016/j.jhep.2018.03.026
48. El Kassas M, Tawheed A, Eltabbakh M, Kaseb A (2019) Hepatitis C antiviral therapy in patients with successfully treated hepatocellular carcinoma: dancing with wolves . *J Hepatocell Carcinoma*. 6:183–191. https://doi.org/10.2147/jhc.s206668
49. El Kassas M, Funk AL, Salaheldin M et al (2018) Increased recurrence rates of hepatocellular carcinoma after DAA therapy in a hepatitis C-infected Egyptian cohort: a comparative analysis. *J Viral Hepat*. 25(6):623–630. https://doi.org/10.1111/jvh.12854
50. Tasleem S, Sood GK (2015) Hepatitis c associated B-cell non-hodgkin lymphoma: clinical features and the role of antiviral therapy. *J Clin Transl Hepatol*. 3(2):134–139. https://doi.org/10.14218/JCTH.2015.00011
51. Arcaini L, Vallisa D, Rattotti S et al (2014) Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. *Ann Oncol*. 25(7):1404–1410. https://doi.org/10.1093/annonc/mdu166
52. Arcaini L, Besson C, Frigeni M et al (2016) Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. *Blood*. 128(21):2527–2532. https://doi.org/10.1182/blood-2016-05-714667
53. Merli M, Frigeni M, Gotti M et al (2017) Direct-acting antivirals during or after immunochemotherapy in hepatitis C virus–positive diffuse large B-cell lymphomas. *Hepatology*. 66(4):1341–1343. https://doi.org/10.1002/hep.29198
54. Torres HA, Shigle TL, Hammoudi N et al (2017) The oncologic burden of hepatitis C virus infection: A clinical perspective. *CA Cancer J Clin*. 67(5):411–431. https://doi.org/10.3322/caac.21403
55. El-Dosouky I, ElHawari S, Emara M, Hamed E (2014) Types and predictors of interferon/ribavirin induced cardiac complications in the egyptian patients with chronic hepatitis C virus. *Zagazig Univ Med J*. 20(5):1–11. https://doi.org/10.21608/zumj.2014.4427
56. Vassalle C, Petta S, Pepe A, et al. Expert opinion on managing chronic HCV in patients with cardiovascular disease Mark Bondin, et al.. Expert opinion on managing chronic HCV in patients with cardiovascular disease Beyond the liver spotlight series: Cardiovascular disease Expert opinion on. *Antivir Ther Int Med Press*. 2018;23(2). doi:10.3851/IMP3248ï
57. Ibrahim MG, Sharafeldin AA, Mousa NI, Mousa TK, El Missiri AM (2020) Effect of direct-acting antivirals on corrected QT interval and cardiac functions in patients with chronic hepatitis C virus infection. *Egypt Hear J*. 72(1). https://doi.org/10.1186/s43044-020-0042-y
58. Adinolfi LE, Nevola R, Guerrera B et al (2018) Hepatitis C virus clearance by direct-acting antiviral treatments and impact on insulin resistance in chronic hepatitis C patients. *J Gastroenterol Hepatol*. 33(7):1379–1382. https://doi.org/10.1111/jgh.14067
59. Butt AA, Yan P, Shuaib A, Abou-Samra AB, Shaikh OS, Freiberg MS (2019) Direct-acting antiviral therapy for HCV infection is associated with a reduced risk of cardiovascular disease events. *Gastroenterology*. 156(4):987–996.e8. https://doi.org/10.1053/j.gastro.2018.11.022
60. Angeletti A, Cantarelli C, Cravedi P (2019) HCV-associated nephropathies in the era of direct acting antiviral agents. *Front Med*. 6(FEB):20. https://doi.org/10.3389/fmed.2019.00020
61. Russo MW (2010) Antiviral therapy for hepatitis C is associated with improved clinical outcomes in patients with advanced fibrosis. *Expert Rev Gastroenterol Hepatol*. 4(5):535–539. https://doi.org/10.1586/egh.10.60
62. Fabrizi F, Donato FM, Messa P (2017) Hepatitis C and its metabolic complications in kidney disease. *Ann Hepatol*. 16(6):851–861. https://doi.org/10.5604/01.3001.0010.5275
63. Gordon CE, Berenguer MC, Doss W et al (2019) Prevention, diagnosis, evaluation, and treatment of hepatitis C Virus infection in chronic kidney disease: Synopsis of the kidney disease: Improving global outcomes 2018 clinical practice guideline. *Ann Intern Med*. 171(7):496–504. https://doi.org/10.7326/M19-1539
64. Gordon CE, Berenguer MC, Doss W et al (2019) Prevention, diagnosis, evaluation, and treatment of hepatitis C virus infection in chronic kidney disease: Synopsis of the kidney disease: Improving global outcomes 2018 clinical practice guideline. *Ann Intern Med*. 171(7):496–504. https://doi.org/10.7326/M19-1539
65. Roth D, Nelson DR, Bruchfeld A et al (2015) Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet*. 386(10003):1537–1545. https://doi.org/10.1016/S0140-6736(15)00349-9
66. Saxena V, Khungar V, Verna EC et al (2017) Safety and efficacy of current direct-acting antiviral regimens in kidney and liver transplant recipients with hepatitis C: results from the HCV-TARGET study. *Hepatology*. 66(4):1090–1101. https://doi.org/10.1002/hep.29258
67. AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2018;67(10):1477–92. https://doi.org/10.1093/cid/ciy585.
68. Dp S, Roesler G, Gj H, Rj P, Arenja N. *Evaluation of pulmonary arterial hypertension in patients with direct-acting antiviral medications for hepatitis C virus infection – a prospective observational cohort study*.; 2019.
69. Younossi Z, Park H, Henry L, Adeyemi A, Stepanova M (2016) Extrahepatic manifestations of hepatitis C: a meta-analysis of prevalence, quality of life, and economic burden. *Gastroenterology*. 150(7):1599–1608. https://doi.org/10.1053/j.gastro.2016.02.039
70. Pungpapong S, Aqel B, Leise M et al (2015) Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. *Hepatology*. 61(6):1880–1886. https://doi.org/10.1002/hep.27770
71. Qing S, Ji D, Li B et al (2015) Improvement of glucose and lipid metabolism with pegylated interferon-α plus ribavirin therapy in Chinese patients chronically infected with genotype 1b hepatitis C virus. *Ann Saudi Med*. 35(4):293–297. https://doi.org/10.5144/0256-4947.2015.293
72. Kaddai V, Negro F (2011) Current understanding of insulin resistance in hepatitis C. *Expert Rev Gastroenterol Hepatol*. 5(4):503–516. https://doi.org/10.1586/egh.11.43
73. Ribaldone DG, Sacco M, Saracco GM (2020) The effect of viral clearance achieved by direct-acting antiviral agents on hepatitis C virus positive patients with type 2 diabetes mellitus: a word of caution after the initial enthusiasm. *J Clin Med*. 9(2):563. https://doi.org/10.3390/jcm9020563
74. Drazilova S, Gazda J, Janicko M, Jarcuska P. Chronic hepatitis C association with diabetes mellitus and cardiovascular risk in the era of DAA therapy. *Can J Gastroenterol Hepatol*. 2018;2018. doi:https://doi.org/10.1155/2018/6150861
75. Modabbernia A, Poustchi H, Malekzadeh R (2013) Neuropsychiatric and psychosocial issues of patients with hepatitis C infection: a selective literature review. *Hepat Mon*. 13(1). https://doi.org/10.5812/hepatmon.8340
76. Ignatova TM, Aprosina ZG, Serov VV et al (1998) Extrahepatic manifestations of chronic hepatitis C. *Ter Arkh*. 70(11):10–16
77. Ramos-Casals M, Muñoz S, Medina F et al (2009) Systemic autoimmune diseases in patients with hepatitis C virus infection: characterization of 1020 cases (The HISPAMEC Registry). *J Rheumatol*. 36(7):1442–1448. https://doi.org/10.3899/jrheum.080874
78. Ramos-Casals M, Jara LJ, Medina F et al (2005) Systemic autoimmune diseases co-existing with chronic hepatitis C virus infection (the HISPAMEC Registry): patterns of clinical and immunological expression in 180 cases. *J Intern Med*. 257(6):549–557. https://doi.org/10.1111/j.1365-2796.2005.01490.x

79. Flores-Chávez A, Carrion JA, Forns X, Ramos-Casals M (2017) Extrahepatic manifestations associated with chronic hepatitis C virus infection. *Rev Esp Sanid Penit*. 19(3):87–97. https://doi.org/10.4321/S1575-06202017000300004
80. Hlaing NKT, Mitrani RA, Aung ST et al (2017) Safety and efficacy of sofosbuvir-based direct-acting antiviral regimens for hepatitis C virus genotypes 1-4 and 6 in Myanmar: Real-world experience. *J Viral Hepat*. 24(11):927–935. https://doi.org/10.1111/jvh.12721
81. Saadoun D, Thibault V, Si Ahmed SN et al (2016) Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVAL-DIC study. *Ann Rheum Dis*. 75(10):1777–1782. https://doi.org/10.1136/annrheumdis-2015-208339
82. Gragnani L, Fabbrizzi A, Triboli E et al (2014) Triple antiviral therapy in hepatitis C virus infection with or without mixed cryoglobulinaemia: a prospective, controlled pilot study. *Dig Liver Dis*. 46(9):833–837. https://doi.org/10.1016/j.dld.2014.05.017
83. Sise ME, Bloom AK, Wisocky J et al (2016) Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. *Hepatology*. 63(2):408–417. https://doi.org/10.1002/hep.28297
84. Roccatello D, Sciascia S, Rossi D et al (2017) The challenge of treating hepatitis C virus-associated cryoglobulinemic vasculitis in the era of anti-CD20 monoclonal antibodies and direct antiviral agents. *Oncotarget*. 8(25):41764–41777. https://doi.org/10.18632/oncotarget.16986
85. Lodi G, Pellicano R, Carrozzo M (2010) Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis. *Oral Dis*. 16(7):601–612. https://doi.org/10.1111/j.1601-0825.2010.01670.x
86. Fachinelli LR, Silva ECRR, De Faria Figueiredo MG, Possa MS, Pelegrinelli FFF, Molina RJ (2012) Hepatite C e alterações cutâneas. *Rev Soc Bras Med Trop*. 45(6):770–773. https://doi.org/10.1590/S0037-86822012000600024
87. Ismail WA, Yousef AE (2019) Effect of sofosbuvir plus daclatasvir for treatment of chronic hepatitis C on patients with psoriasis. *Eur J Gastroenterol Hepatol*. 31(8):1025–1029. https://doi.org/10.1097/MEG.0000000000001370
88. Berk DR, Mallory SB, Keeffe EB, Ahmed A (2007) Dermatologic disorders associated with chronic hepatitis C: effect of interferon therapy. *Clin Gastroenterol Hepatol*. 5(2):142–151. https://doi.org/10.1016/j.cgh.2006.06.010
89. Gisbert JP, García-Buey L, Pajares JM, Moreno-Otero R (2003) Prevalence of hepatitis C virus infection in porphyria cutanea tarda: Systematic review and meta-analysis. *J Hepatol*. 39(4):620–627. https://doi.org/10.1016/S0168-8278(03)00346-5
90. Singal AK, Kormos-Hallberg C, Lee C et al (2012) Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda. *Clin Gastroenterol Hepatol*. 10(12):1402–1409. https://doi.org/10.1016/j.cgh.2012.08.038

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