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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Impact of Direct Acting Antiviral Agent Therapy upon Extrahepatic Manifestations of Hepatitis C Virus Infection

Arpan Mohanty[1] · Sarah Salameh[2] · Adeel A. Butt[2,3,4,5]

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Abstract

Purpose of Review Direct acting antiviral agents (DAAs) have emerged as simple, short, safe, and effective treatments for chronic hepatitis C (CHC) infection. CHC is a systemic disease with frequent and multiple extrahepatic manifestations. The beneficial effects of DAA treatment regimens extend beyond improvement in liver-related outcomes to amelioration of extra hepatic manifestations and are likely to have economic implications. The purpose of this review is to evaluate the effect of DAAs on extra hepatic manifestations of CHC virus infection.

Recent Findings Recent studies indicate that DAAs are associated with reduction in all-cause mortality, even in patients without significant hepatic fibrosis. They are also associated with reduction in incident cardiovascular disease and diabetes. DAAs are the mainstay of treatment in HCV-associated cryoglobulinemia and lymphoma. Successful HCV therapy with DAAs also improves patient-related outcomes such as health-related quality of life.

Summary DAAs improve extrahepatic manifestations of CHC virus infection. Future studies are needed to evaluate the long-term durability of treatment response and for accounting amelioration of extrahepatic manifestations into the cost effectiveness of DAA regimens.

Keywords DAA · HCV · SVR · Extrahepatic manifestation · Outcome · Epidemiology

Abbreviations

DAA	Directly acting antiviral agents
CHC	Chronic hepatitis C
HCV	Hepatitis C virus
PROs	Patient-related outcomes
HRQOL	Health-related quality of life
VA	Veterans Affairs
SVR	Sustained virologic response
MC	Mixed cryoglobulinemia
NHL	Non-Hodgkin's lymphoma
DLBCL	Diffuse large B cell lymphoma
HbA_{1C}	Hemoglobin A_{1C}
CVD	Cardiovascular disease
CKD	Chronic kidney disease

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✉ Adeel A. Butt
aab2005@qatar-med.cornell.edu

[1] Boston University School of Medicine, Boston, MA, USA

[2] Hamad Medical Corporation, Doha, Qatar

[3] VA Pittsburgh Healthcare System, Pittsburgh, PA, USA

[4] Weill Cornell Medical College, New York, NY, USA

[5] Weill Cornell Medical College, Doha, Qatar

Introduction

Chronic hepatitis C (CHC) virus infection is estimated to affect 71 million individuals worldwide and leads to approximately 399,000 deaths from liver cirrhosis and hepatocellular carcinoma [1]. Apart from the hepatic complications, CHC is a systemic disease with myriad extrahepatic manifestations associated with poorer clinical outcomes [2, 3] and a significant economic burden [4, 5]. These include mixed cryoglobulinemia, extrahepatic malignancies, and rheumatologic, cardiovascular, renal, endocrine, and neurocognitive effects [6–8]. CHC also affects patient reported outcomes (PROs) such as fatigue and health-related quality of life (HRQOL) [9].

Direct acting antiviral agents (DAAs) have emerged as simple, short, safe, and effective regimens, changing the landscape of hepatitis C virus (HCV) treatment. DAA regimens have been established to improve liver-related outcomes, such as reduction in the risk of cirrhosis, decompensated liver disease, hepatocellular carcinoma, and all-cause mortality [10–13]. This review aims to evaluate the effect of DAAs on extra hepatic manifestations of HCV.

Effect on All-Cause Mortality

Reduction in all-cause mortality is the fundamental aim of HCV therapy. In a propensity matched study from the Department of Veterans Affairs (VA), Butt et al. demonstrated that DAA regimens (sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir/dasabuvir) were associated with 57% reduction in all-cause mortality that was apparent in the first 18 months post treatment [11]. Twenty-five per cent of the study population had cirrhosis (as defined by FIB 4 > 3.25). Attainment of sustained virologic response (SVR) was associated with 43% reduction in mortality. In another observational study from the VA, Backus et al. analyzed the effect of SVR in response to DAAs on all-cause mortality in individuals with CHC virus infection without cirrhosis (defined as FIB < = 3.25) [10]. Sixty-five per cent of the individuals in this study received a sofosbuvir/ledipasvir-based regimen. Even in individuals without cirrhosis, SVR was associated with 69% decrease in all-cause mortality as compared to untreated patients and 59% reduction in mortality in comparison to patients treated with DAAs who did not achieve SVR, after adjusting for covariates. The observation remained true in the subset of persons with FIB 4 < 1.45 (which is recognized as the threshold to exclude significant fibrosis), highlighting the importance of treating all patients with HCV and not just those with advanced fibrosis.

Effect on Mixed Cryoglobulinemia

Mixed cryoglobulinemia (MC) is a common extrahepatic manifestation of CHC virus infection characterized by HCV antigen-driven B cell clonal proliferation leading to deposition of circulating immune complexes in small vessels of the skin, nerves, kidney, liver, and joints. HCV accounts for 85–95% of all cases of MC [14, 15]. While up to 50% of patients with CHC virus infection have circulating cryoglobulins, only about 10–15% have clinical manifestations which include palpable purpura, arthralgias, neuropathy, and glomerulopathy [16]. The mainstay of treatment for HCV-associated MC is anti-HCV therapy. In addition, some patients may need plasma exchange, steroids, and rituximab. Improvement and resolution of MC with interferon-based therapies is well established [17]. However, interferon-based therapies in CHC virus–infected patients with MC was associated with lower rate of SVR and significant side-effects as compared to patients without MC [17]. Newer DAA regimens in patients with MC achieve higher SVR rates (83–100%), comparable to patients without MC suggesting that presence of cryoglobulins itself may not be the main driver of treatment failure [18–22]. The lack of side-effects, including the immune-stimulatory effects seen with interferon use, have made DAAs the drug of choice for HCV-associated MC [8]. DAA regimens for HCV-associated MC are associated with a lesser need for supplemental steroids and rituximab [21, 23]. Attainment of SVR with DAA regimens correlates with clinical improvement in symptoms. It is however important to note that the clinical and immunologic response to DAA therapies in HCV-associated MC may lag behind SVR. Emery et al. reported that in 16/18 patients with symptomatic cryoglobulinemic vasculitis who achieved SVR, only 7 (38.8%) had complete resolution of symptoms in a median follow-up time of 5 months [20]. Similar results were reported by Sadoun et al. and Gragnani et al. where all patients achieved SVR [21, 23]. Bonacci et al. also showed that a low cryocrit (< 2.7%) was associated with complete immunologic response as defined by undetectable cryoglobulins and complement and rheumatoid factor normalization [18]. In a recent larger, long-term follow-up study of 148 patients (median follow-up of 15.3 months), 72.6% patients had complete response, 22.6% had partial response, and 4.8% had no response [19]. Skin and renal manifestations are more likely to resolve as compared to neurologic manifestations, some of which may be irreversible due to permanent nerve damage. In CHC virus infection–associated MC, DAA regimens have also been shown to improve disturbances in B and T cell homeostasis [24]. Restoration of this imbalance may thus in part underlie the mechanisms treating this primarily autoimmune disease, a role beyond achieving SVR. However, in some instances of HCV-associated MC, cryoglobulinemia may persist or relapse after SVR [25]. Studies with longer follow-up are needed to establish the durability of clinical and immunologic response, especially in patients with severe manifestations. Overall, studies in the DAA era support the early initiation of DAA therapy in HCV-associated MC to prevent permanent and future complications.

Effect on HCV-Associated Lymphoma

In addition to MC, CHC virus infection is associated with a spectrum of lymphoproliferative processes. The association of certain types of B cell non-Hodgkin's lymphoma (NHL) with HCV is well reported in epidemiological studies and corroborated by lymphoma regression with interferon-based therapies [26–30]. A meta-analysis evaluating the correlation of SVR (from interferon-based regimens) with lymphoma

regression in patients with HCV-associated B cell NHL found that SVR was strongly associated with lymphoma response (83% vs 53%) [29]. B cell NHL may develop from a background of MC or independently. In patients with continued clinical manifestations of MC after successful HCV therapy, B cell lymphomas should be considered [31, 32].

In the DAA era, a large case series of patients with HCV and associated lymphoproliferative disorders (37/46, i.e., 80% patients with marginal zone lymphoma) reported 98% SVR with DAA regimens [33]. Lymphoma regression was seen in 67% patients including 26% patients with complete response and 12% patients with partial response. High SVR rates and safety of DAAs with concomitant chemotherapy for HCV-associated and non-HCV–associated malignancies were also noted in other smaller studies [34, 35]. A recent study by Persico et al. compared disease-free survival of a cohort of 20 CHC virus–infected patients who received DAA regimens along with chemotherapy for diffuse large B cell lymphomas to a historic retrospective CHC virus–infected diffuse large B cell lymphomas cohort who did not receive antiviral therapy with chemotherapy [36]. In a follow-up period of 52 weeks, disease-free survival was significantly improved in patients treated with DAA regimens compared to untreated patients ($p = 0.036$). Larger population-based studies are needed to study the effect of DAA regimens on risk of lymphomas.

Effect on Diabetes and Metabolic Syndrome

CHC virus infection is associated with increased prevalence as well as increased risk of incident diabetes mellitus. While there were conflicting reports on the effect of interferon-based therapies on incident diabetes and glycemic control, DAA regimens have has been associated with beneficial effects. Diabetic patients undergoing treatment with DAA regimens have been shown to have better fasting glucose, glycated hemoglobin (hemoglobin A_{1C}/HbA_{1C}), and decreased requirement of antidiabetic drugs during anti-HCV therapy as well as after attaining SVR [37–40]. Beneficial effects of DAA regimens on glycemic control have also been seen in post-liver transplant patients with recurrent HCV [41]. Hum et al. evaluated the effect of SVR in response to DAAs (without the use of ribavirin) on glycemic control as determined by HbA_{1C} in over 2400 patients with diabetes mellitus and elevated HbA_{1C} [42]. While pre-treatment HbA_{1C} was comparable in patients who attained SVR and those who did not, there was greater decline in HbA_{1C} (− 0.98%) in those who attained SVR as compared to those who did not (− 0.65%). In a recent large study of 21,279 CHC virus–infected persons, DAA therapy was associated with a 52% reduction in incidence of diabetes (HR 0.48, 95%CI 0.42, 0.56) while attainment of SVR was associated with a 19% reduction in incidence of diabetes (HR 0.81, 95%CI 0.70, 0.93) compared with untreated persons. Those with more advanced fibrosis had a greater risk reduction compared with early or no fibrosis. Pegylated interferon-based regimens were not associated with a reduced risk of incident diabetes compared with untreated controls [43].

Effect on Cardiovascular Disease

Chronic hepatitis C (CHC) virus infection is independently associated with increased risk of cardiovascular disease (CVD). After adjusting for other risk factors, CHC infection is associated with a 27% increase in risk of CVD events compared with uninfected controls [44]. HCV-related atherosclerotic risk also has basis in pro-atherogenic mechanisms, demonstrated in carotid plaques [45–47] as well as differential prevalence of traditional CVD risk factors such as insulin resistance and diabetes [48]. In a recent study of 12,667 DAA-treated persons and CVD-risk matched controls (based on baseline atherosclerotic cardiovascular disease score), DAA treatment was associated with a 43% reduction in risk of incident CVD events [49]. The same study also demonstrated a 22% reduction in risk of incident CVD events among those treated with a pegylated interferon plus ribavirin regimen. Attainment of SVR was associated with a 13% reduction in risk compared with those who did not attain SVR.

There is limited understanding on how HCV therapy ameliorates risk of cardiovascular disease. In a prospective study, Petta et al. evaluated changes in carotid atherosclerosis in patients with advanced liver fibrosis/cirrhosis undergoing anti-HCV therapy with DAA-based regimens [50]. They demonstrated decrease in intimal medial thickness 9–12 months after completion of therapy. The results held true when patients were stratified by cardiovascular risk factors and liver disease severity. Further studies are needed to understand the interaction of HCV therapy and resultant changes in metabolic factors on cardiovascular outcomes.

Effect on Renal Disease

CHC virus infection is associated with classic renal complications such as albuminuria and glomerulonephritides [51, 52]. However, there is conflicting evidence on the effect of CHC virus infection on incident kidney disease and worsening of pre-existing kidney disease. A study from a large VA cohort between 2001 and 2014 compared newly seroconverted HCV-infected Veterans with HCV-uninfected Veterans. CHC virus infection was associated with decreased incidence of advanced chronic kidney disease (CKD; CKD stage 3–5) and unchanged risk of progression of CKD (decline in estimated glomerular filtration rate > 30 mL/min/1.73 m^2) [53]. While

lack of association of HCV with renal disease has been reported in some studies [54, 55], other studies including a large meta-analysis have supported this association [56–59]. There are limited data on the effect of DAA regimens on renal function in CHC virus–infected individuals. In a small, single-center study, patients who achieved SVR in response to DAA therapy were compared to a retrospective cohort of untreated HCV-infected patients. There was no significant difference in renal function decline between these groups after a short-term follow-up of 1–2 years [60]. Larger studies with longer term follow-up are warranted to establish the effect of DAA based HCV therapy on renal function.

Effect on Health-Related Quality of Life (HRQOL) and Patient Reported Outcomes

Chronic pain, fibromyalgia, and fatigue are common symptoms in patients with CHC virus infection and affect HRQOL, in both patients with and without significant fibrosis. These manifestations of CHC virus infection add to the economic burden by direct healthcare costs and loss of productivity. In clinical trials of DAA regimens, patient-related outcomes (PROs) have been assessed by standardized questionnaires and suggest short-term benefits of these regimens on PROs. Their generalizability to the real-world setting and the long-term sustainability of improvements in PROs is unclear. Early in the DAA era, Younossi et al. compared PROs in patients who received interferon, sofosbuvir, and ribavirin (genotype1) to those who received sofosbuvir and ribavirin (genotype2/3) and showed PROs are adversely affected by use of interferon during treatment [61, 62]. Patients who achieved SVR had significant improvement in PROs regardless of the regimen used. In subsequent clinical trials in cirrhotic as well as non-cirrhotic patients (ION and ASTRAL trials), similar results were seen [63–65]. In addition, SVR was associated with improvement in HRQOL regardless of fibrosis stage [66]. Mixed PRO response was noted during treatment with DAA regimens containing ribavirin [63–65, 67]. But PRO response was comparable in few weeks after attainment of SVR in both ribavirin-free and ribavirin-containing regimens suggesting that the effect of ribavirin on PROs is transient, likely to be secondary to anemia. In an analysis of blood samples of 100 patients undergoing treatment in these trials, central fatigue and peripheral fatigue was noted to be associated with different markers [63]. Reductions in levels of chemokine ligand 2 were associated with persistence of fatigue after SVR. Long-term follow-up studies on trial patients are needed to provide information on the durability of PRO response.

Summary

In addition to liver-related complications, CHC virus infection is associated with multiple extra hepatic manifestations which increase the morbidity and mortality burden. DAA regimens have changed the landscape of HCV management by making treatment safer, tolerable, and more effective. In addition to viral long-term viral eradication, treatment with DAA regimens is associated with reduction in all-cause mortality, cardiovascular, metabolic, renal, and hematologic/oncologic complications, as well as improvement in HRQOL. Improvement in extrahepatic outcomes is additional strong evidence to advocate treatment for all CHC virus infected persons.

Compliance with Ethical Standards

Conflict of Interest No potential conflicts of interest relevant to this article were reported.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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