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Impact of DAA-Based Regimens on HCV-Related Extra-Hepatic Damage: A Narrative Review

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Abstract

Two-third of patients with chronic hepatitis C show extrahepatic manifestations due to HCV infection of B lymphocytes, such as mixed cryoglobulinemia and non-Hodgkin B-cell lymphoma, or develop a chronic inflammatory status that may favor the development of adverse cardiovascular events, kidney diseases or metabolic abnormalities.

DAAs treatments induce HCV eradication in 95% of treated patients, which also improves the clinical course of extrahepatic manifestations, but with some limitations. After HCV eradication a good compensation of T2DM has been observed, but doubts persist about the possibility of obtaining a stable reduction in fasting glucose and HbA1c levels.

Chronic HCV infection is associated with low total and LDL cholesterol serum levels, which however increase significantly after HCV elimination, possibly due to the disruption of HCV/lipid metabolism interaction. Despite this adverse effect, HCV eradication exerts a favorable action on cardiovascular system, possibly by eliminating numerous other harmful effects exerted by HCV on this system.

DAA treatment is also indicated for the treatment of patients with mixed cryoglobulinemia syndrome, since HCV eradication results in symptom reduction and, in particular, is effective in cryoglobulinemic vasculitis. Furthermore, HCV eradication exerts a favorable action on HCV-related lymphoproliferative disorders, with frequent remission or reduction of clinical manifestations.

There is also evidence that HCV clearance may improve impaired renal functions, but same conflicting data persist on the effect of some DAAs on eGFR.

Keyword

HCV extrahepatic manifestations · Hepatitis C virus · Interferon-free DAA regimens

1 Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide. Chronic HCV infection tends to progress towards liver fibrosis and cirrhosis and subsequently to hepatocellular carcinoma (HCC) in the context of bridging fibrosis or liver cirrhosis (Stroffolini et al. 2018; Sagnelli et al. 2013, 2019).

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In 2015, 71 million people were living with chronic HCV infection worldwide (Global Hepatitis Report 2017). Exposure to infected blood or blood products (intravenous drug use, iatrogenic exposure, tattooing, piercing) and risky sexual contact (multiple partners, anal sex, presence of genital lesions) were the risk factors most frequently associated with the transmission of this infection (Santantonio et al. 2006; Corey et al. 2006; Daniels et al. 2009; Esteban et al. 2008).

After becoming infected with HCV, almost 35% of the subjects eliminate the virus spontaneously or after asymptomatic acute self-limiting hepatitis, while the remaining 65% progress to chronicity, identifiable by the persistence of HCV RNA in serum for at least 6 months (Alter et al. 1992). The natural history of chronic HCV infection is extremely variable, from a long-term absence of liver lesions to the persistence of minimal liver changes with a slow indolent progression to fibrosis or a rapid progression to liver cirrhosis and its serious complications, such as portal hypertension, liver failure and HCC development (Poynard et al. 1997, 2000). Several factors can accelerate the progression of liver disease, including an older age at the time of infection, concomitant alcohol abuse, presence of diabetes and coinfection with HIV and/or HBV (Alter et al. 1992; Poynard et al. 1997, 2000; Alter and Seeff. 2000; Coppola et al. 2012, 2014, 2015; Webster et al. 2015; Bagaglio et al. 2020; Sagnelli et al. 2020).

Nearly two-thirds of patients with chronic HCV infection (CHC) show extrahepatic manifestations due to HCV infection of B lymphocytes, such as mixed cryoglobulinemia and non-Hodgkin B-cell lymphoma, or to a chronic inflammatory status that may favor the development of adverse cardiovascular events (stroke, coronary artery disease), kidney diseases and metabolic abnormalities (Cacoub et al. 2014; Calogero et al. 2019).

Interferon (INF) alfa was the cornerstone of chronic HCV therapy until 2014, but was later replaced by classes of direct acting antiviral agents (DAA) which, combined with each other, give much better therapeutic results and a marked reduction in treatment times and adverse reactions. Today, thanks to the high and rapid effect of DAA regimens, the sustained virological response rate at the twelfth post-treatment week (SVR12) is about 95%, even in the presence of advanced liver diseases (EASL Recommendations on Treatment of Hepatitis C 2018).

Although the effectiveness of DAA combinations on the eradication of HCV infection is proven by numerous randomized clinical trials and by a day to day worldwide clinical practice, their efficacy on the associated metabolic disorders and related extrahepatic manifestations need further clarification.

2 Chronic Inflammatory Status and Extra-Hepatic Damage

The pathogenesis of extra-hepatic manifestations of HCV infection has not been fully investigated at present (Fletcher and McKeating 2012; Zignego et al. 2007). HCV infection determines the clonal expansion of B lymphocytes (Carbonari et al. 2005; Charles et al. 2008) with the production of rheumatoid factor M immunoglobulin (Ig), which in sensitive subjects causes the deposition of immune complexes in small vessels, with consequent vasculitis. The mechanisms of other manifestations seem multifactorial, including a direct interaction between viral proteins and intracellular signaling pathways, viral replication in extra-hepatic cells and an intensified immune reaction with systemic effects. The activation of the immune system may induce chronic inflammation as occurs in human immunodeficiency virus (HIV) infection (Kuller et al. 2008; Petta et al. 2014; Negro 2014; Negro et al. 2015; Bedimo and Abodunde 2016).

Patients with chronic HCV infection are at risk of developing type 2 diabetes mellitus (T2DM), the most common extra-hepatic manifestation in this infection (Mehta et al. 2000; Wang et al. 2007; Vanni et al. 2016; Mehta et al. 2000). In addition, compared with uninfected controls, HCV infected patients more frequently show high levels of insulin resistance (IR) (Moucari et al. 2008; Younossi et al. 2013). On the other

hand, compared with untreated subjects, HCV-infected patients more frequently show a cardioprotective lipid profile, characterized by significantly lower levels of serum total cholesterol, low-density lipoprotein, and triglycerides (TC) and higher serum levels of high-density lipoprotein (Vassalle et al. 2004; Dai et al. 2008). Nonetheless, data from several studies show an association between HCV infection and atherosclerotic damage (Vassalle et al. 2004; Marzouk et al. 2007; Targher et al. 2007; Dai et al. 2008; Alyan et al. 2008; Petta et al. 2012; Hsu et al. 2015b) with increased mortality by circulatory diseases (Lee et al. 2012). These conflicting data deserve careful and thorough investigation.

It has also been observed that, compared to the general population, HCV-positive subjects more frequently develop chronic kidney disease (CKD) (Latt et al. 2012).

Studies have shown that therapy to eradicate HCV infection improves some extra-hepatic manifestations associated with HCV infection, regardless of the severity of liver disease. The evidence is stronger for mixed cryoglobulinemia, which often resolves entirely with viral clearance (Mazzaro et al. 1996; Cacoub et al. 2005; Dammacco and Sansonno 2013), but it remains unclear for extra-hepatic manifestations due to the chronic inflammatory state which have often been considered contraindications to INF-based treatment for the possibility of their exacerbation, for possible drug interaction with drugs used to treat them or for fear of additional toxicity (Massoumy et al. 2013; Kanwal et al. 2014). The directly acting antiviral (DAA) regimens are more effective and better tolerated than interferon-based therapy and therefore more frequently usable in the presence of extra-hepatic manifestations.

The purpose of this narrative review is to provide an overview of the knowledge available on the action exerted by DAA therapy on the extra-hepatic manifestations of chronic HCV infection. The article is addressed to all young doctors, to all doctors working in infectious diseases, gastroenterology, and internal medicine wards and to general practitioners who aid patients with chronic HCV infection.

3 Methods

We conducted a computerized bibliographic search using MEDLINE and EMBASE involving both medical title terminology (MeSH) and relevant keywords for search strings to locate studies that analyzed until April 2020 the outcome of HCV patients after DAA treatment. The following items were used for research in the studies: "hepatitis c", "HCV", "direct active antivirals", "DAA" and "kidney", "eGFR", "kidney function", "diabetes", "glycemic control", "blood sugar", "lipids", "triglycerides", "cardiovascular", "median intimal thickness", "hypertension", "lymphoma", "B-NHL", "DLBCL", "CHL", "Mixed Cryoglobulinemia Syndrome", "vasculitis". Based on the main research objectives, the articles were classified into one of the following research topics: kidney function, glycemic control, lipid control and cardiovascular events.

4 DAAs and Glycemic Homeostasis

The correlation between alterations in the glycid balance and CHC is made evident by the frequent development (30–70%) of insulin resistance in CHC patients, by the 3.8 times higher rate of chronic HCV infection in patients with T2DM than in those without (Vanni et al. 2016), by the more frequent progression of fibrosis in patients with CHC and IR (Hui et al. 2003) and by a more frequent development of HCC (Desbois and Cacoub 2017) in patients with CHC and T2DM than in those with CHC alone. The eradication of HCV infection with IFN-alfa therapy induces a substantial improvement in the markers of glucose metabolism as shown in a meta-analysis (Cacoub et al. 2018a) on 7,000 CHC patients from 40 studies; after IFN treatment, the incidence of IR and T2DM was significantly reduced during a long-term post-treatment follow-up in those who achieved a sustained virological response (SVR). In a retrospective study performed in Japan on 2,842 CHC patients treated with IFN the rate of T2DM was 3.6% at

the 5th year, 8.0% at the 10th year and 17.0% at the 15th year of post-treatment observation, predictive factors for T2DM development being advanced liver disease, failure to achieve SVR after treatment and age of 50 or more years (Arase et al. 2009). In a retrospective study from Spain on 234 IFN treated CHC or liver cirrhosis patients, glucose abnormalities occurred less frequently in those who obtained SVR than in those who did not (14.6% versus 34.1%) (Simó et al. 2006).

Contrasting data comes from an Italian retrospective study (Giordanino et al. 2008) where no association was found between SVR and a lower risk of developing T2DM during an 8-year follow-up.

A substantial improvement in fasting glucose and glycosylated hemoglobin levels were observed in HCV patients who achieved SVR with DAA treatment (Bose and Ray 2014; Meissner et al. 2015; Pavone et al. 2016; Morales et al. 2016; Hum et al. 2017; Ikeda et al. 2017; Fabrizio et al. 2017; Abdel Alem et al. 2017; Dawood et al. 2017; Ciancio et al. 2018; El Sagheer et al. 2018), regardless of the DAA regimen used (Meissner et al. 2015; Pavone et al. 2016; Morales et al. 2016; Abdel Alem et al. 2017; Fabrizio et al. 2017; Ikeda et al. 2017; Dawood et al. 2017; Ciancio et al. 2018; El Sagheer et al. 2018) (Table 1). In a National Veterans Health System study on 2435 HCV patients treated with different DAA regimens, a significantly higher reduction in mean hemoglobin A1c (HbA1c) was observed in the 2180 who achieved SVR compared to the 275 non-SVR-patients (Hum et al. 2017).

In a study on 91 HCV-positive liver transplant patients, 96% achieved SVR and HbA1c dropped from 35.5 ± 4.3 mmol/L to 33.3 ± 3.6 mmol/L at the 44th week after treatment; in patients not treated with anti-diabetic agents, a fasting glucose level decreased from 6.8 ± 1.7 mmol/L before antiviral therapy to 5.7 ± 1.1 mmol/L at the 24th week after treatment discontinuation (Beig et al. 2018).

The association between SVR induced by DAA regimens and glycaemic control is further supported by the behaviour of other parameters, like IR development, T2DM development and type and doses of anti-diabetic drugs. A prospective study showed that HCV eradication produced a clearance or reduction of IR in 76% of 133 non-diabetic HCV-genotype 1 patients with advanced liver disease who achieved SVR12 (Adinolfi et al. 2018a, b). The DAA-induced SVR also correlates with a reduced risk of developing TDM2 (Adinolfi et al. 2018a) and with an improvement in glycemic control in T2DM patients (Adinolfi et al. 2018a). In addition, HCV patients with T2DM receiving oral anti-diabetic or insulin treatment needed a dose reduction during DAA therapy (Soriano et al. 2016; Hum et al. 2017; Ikeda et al. 2017; Ciancio et al. 2018; Teegen et al. 2019). Compared to the baseline values, a significant improvement in beta-cell function was observed after DAA treatment in a prospective, open-label, multi-center study (107.7 ± 86.8 vs. 86.7 ± 44.5, $p = 0.05$), an improvement more evident in patients with high baseline IR (Huang et al. 2017). A post hoc analysis of six studies on CHC genotype-1 patients with advanced fibrosis showed a significant reduction in fasting glucose levels in patients treated with paritaprevir/ritonavir/ombitasvir/dasabuvir, compared to those in the placebo group (Tran et al. 2017): the most significant reduction being observed in T2DM patients (22.1 mg/dL less at the 12th week compared to the baseline), followed by those in a pre-diabetic status (−5.78 mg/dL by week 12) (Tran et al. 2017). As for the HbA1c, a substantial reduction was observed only in responders with a high baseline HbA1c level (Hum et al. 2017). In addition, in an Egyptian study on CHC patients with HCV genotype-4 and T2DM who achieved SVR, the independent prognostic factors for a drop in blood glucose levels >20 mg/dl or a drop in HbA1c levels >0.5% were a T2DM duration less than 7 years, a T2D negative family history and a liver disease severity up to cirrhosis Child-Pugh A (Dawood et al. 2017). Pavone et al. retrospectively evaluated 21 HCV-positive patients with T2DM treated with different interferon-free DAA regimens; fasting glucose serum levels significantly decreased during treatment (mean value −52.86 mg/dL, $p = 0.007$); also glycated

Table 1 Changes in glycemic balance in DAA treated CHC patients

References	Type of study	Number of patients, Setting	HCV-Genotype	Treatment	Results
Meissner et al. (2015)	Cohort study	55 HCV-T2DM patients	HCV-G 1a/b	SOF/RBV	Decrease in HbA1c.
Morales et al. (2016)	Observational retrospective study	60 CHC patients, of whom 38.3% with T2DM	HCV-G-1a/b	SOF-based regimens	Decrease in HbA1c; reduced doses of antidiabetic drugs in 25% of cases.
Pavone et al. (2016)	Observational retrospective	149 CHC patients, of whom 19% with T2DM	12.1% HCV-G 1	SOF-based regimens	Decrease in FGL, decrease in HbA1c; reduced doses of antidiabetic drugs in 23% of cases.
Abdel Alem et al. (2017)	Retrospective observatinal study	65 CHC-T2DM patients	Most cases with HCV-G4	SOF-based regimens	Decrease in FGL, HbA1c decrease.
Fabrizio et al. (2017)	Observational retrospective study	449 CHC patients, of whom 13.1% with T2DM and 2.0% with HIV coinfection	1.3% HCV-G 1a 6.5% HCV-G 1b	SOF/RBV 32.2% SOF/ SIM ± RBV 13.5% SOF/ LED±RBV 25.4% OMV/PTV/r/ DSV ± RBV 27.1% SOF/DCV/ RBV 1.6%.	Decrease in FGL.
Hum et al. (2017)	Observational retrospective study	2,435 CHC-T2DM patients	99.3% HCV-G 1	SOF/SMV SOF/LED OMV/PTV/r/ DSV	Decrease in HbA1c, reduced doses of antidiabetic drugs in 9% of cases.
Dawood et al. (2017)	Clinical trial open labeled	460 CHC patients, of whom 82.2% with T2DM	HCV-G 4	SOF/DCV	Decrease in FGL, decrease in HbA1c; reduced doses of antidiabetic drugs in 27% of cases.
Ikeda et al. (2017)	Observational prospective study	36 CHC patients, of whom 36.1% with T2DM	HCV-G 1b	SOF/LED	Decrease in HbA1c.
Stine et al. (2017)	Retrospective cohort study	165 CHC patients, of whom 18.5% with T2DM	80.8% HCV-G 1	SOF/LED 38.5% SOF/SIM 26.9% SOF/RBV 19.2% SOF/RBV/peg-INF 7.8% SOF/LED/ RBV 3.9% BOC/RBV/ peg-INF 3.9%	No decrease in HbA1c; reduced doses of antidiabetic drugs in 13% of cases.

(continued)

Table 1 (continued)

References	Type of study	Number of patients, Setting	HCV-Genotype	Treatment	Results
Huang et al. (2017)	Prospective study	65 CHC patients, of whom 21.7% with T2DM	72.3% HCV-G 1 27.7% HCV non-G 1	SOF-based regimens 46.2% PTV-OMV/ DSV/r 35.4% ASV/DCV 18.5%	Significant improvement in beta-cell function, mainly if high basal insulin resistance.
Ciancio et al. (2018)	Observational prospective study	122 CHC patients, of whom 82.8% with T2DM	4% HCV-G 1a 54.5% HCV-G 1b	SOF/ SMV ± RRV 20% SOF/LED ± RBV 41.8% SOF/ DCV ± RBV 10% SOF/RBV 11.8% OMV/PTV r/DSV ± RBV 10.9% OMV/PTV/ r ± RBV 5.5%	Decrease in FGL, decrease in HbA1c; reduced doses of antidiabetic drugs in 21% of cases.
Beig et al. (2018)	Observational retrospective study	91/132 (69%) patients with recurrent HCV infection after liver transplantation, of whom 41.8% with T2DM	51.5% HCV-G 1	SOF/LED ±RBV 60% SOF/ RBV ± PEG 21% G/P 7% SOF/VEL 5% Viekira Pak 3% SOF/ DCV ± RBV 3%	Decrease in FGL and HbA1c; reduced doses of antidiabetic drugs in 40% of cases.
Drazilova et al. (2018)	Longitudinal retrospective observational study	370 CHC patients, of whom 10.2% with T2DM	78.8% HCV-G 1b 11.9% HCV-G 1a	SOF based regimens OMV/PTV/r/ DSV EBR /GZR	Decrease in FGL, reduced doses of antidiabetic drugs in 17.6% of cases.
Chaudhury et al. (2017)	Prospective, longitudinal cohort study	251 CHC patients, of whom 17% with T2DM, and 31% with HIV coinfection	HCV-G 1	DAA/IFN/ RBV 14% DAA/RBV 16% DAA 70%	No decrease in HbA1c, reduced doses of antidiabetic drugs in 3% of cases.
Weidner et al. (2018)	Observational retrospective study	281 CHC patients, of whom 10.0% with T2DM	72% HCV-G 1	DAA ± RBV	Decrease in FGL, HbA1c decrease.
El Sagheer et al. (2018)	Cohort study	80 CHC patients	*HCV-G* 4	SOF + SMV	Decrease in FGL.
Butt et al. (2019)	Retrospective case control study	17,103 CHC patients without a diagnosis of any CVD and a control group	//	PEG-RBV regimen 26% DAA regimens 74%	More significant reduction in T2DM incidence rate in patients treated with DAAs

(continued)

Table 1 (continued)

References	Type of study	Number of patients, Setting	HCV-Genotype	Treatment	Results
		with a number equal to case group			compared to other PEG-RBV regimen or untreated.
Lanini et al. (2019)	Retrospective cohort study	205 CHC patients, of whom 26.3% with T2DM and 15.6% with HIV coinfection	27.37% HCV-G 1a 37.56% HCV-G 1b	SOF/LED± RBV 35.61% 2D/3D ± RBV 3.41% SOF/ DAC ± RBV 19.51% SOF/ SIM ± RBV 28.78% SOF/RBV 12.68%	Decrease in FGL.
El Serag et al. (2019)	Retrospective cohort study	45,260 CHC patients	*57.7% HCV-G1a 26.7% HCV-G1b 9% HCV-G2 5.1% HCV-G3 0.95% HCV-G4 0.07% HCV-G5/G6*	SOF ± LDP 81.76% OMV/DSV/r 14.85% EBR/GZR 2.44% SIM 6.25% DVC 1.6%	Incidence of DM between the SVR and the non-SVR group did not significantly differ.
Gilad et al. (2019)	Observational retrospective study	122 CHC-T2DM patients		DAA	Decrease in HbA1c in 34% of cases.
Teegen et al. 2019	Observational retrospective study	100 patients with HCV -recurrence after LT	84% HCV-G 1	SOF/LDV RBV 53% SOF/SMV 22% SOF/DCV 21% SOF/RBV 2% OMV/PTV/r 2%	Significant decline in the daily average insulin dose.
Li et al. (2019)	Observational retrospective/ prospective study	192 CHC-T2DM patients	67% HCV-G 1	DAA	Decrease in HbA1c.
Alicia Halim Wong et al. (2020)	Retrospective observational study	996 CHC patients, of whom 22% with T2DM	87.1% HCV-G 1	LDV/SOF 89.6% SOL/VEL 7.8% EBR /GZR 2.6%	Decrease in HbA1c by 0.04%.

CHC Chronic Hepatitis C (some cirrhotic cases are included), *SVR* sustained viral response, *FGL* fasting glucose level, *HbA1c* hemoglobin A1c, *Peg-IFN* pegylated-interferon, *RBV* ribavirin, *HIV* human immunodeficiency virus, *OMV* ombitasvir, *PTV* paritaprevi, *r* ritonavir, *DSV* dasabuvir, *G/P* glecaprevir/pibrentasvir, *SOF* sofosbuvir, *SIM* simeprevir, *LDV* ledipasvir, *DCV* daclatasvir, *ASV* asunaprevir, *EBR* elbasvir, *GZR* grazoprevir, *VEL* velpatasvir, *T2DM* type 2 diabetes mellitus

haemoglobin values (detected in 10 patients at weeks 4, 8 and/or 12) significantly decreased during treatment (−1.95%, $p = 0.021$). The Authors concluded that diabetes could be considered as an element to prioritize treatment in CHC patients (Pavone et al. 2016). Soriano et al. described a significant decrease in fasting serum glucose level during DAA treatment in a CHC patient with T2DM, an event forcing a reduction in insulin dosage (Soriano et al. 2016). Also, in a Teegen's study on liver transplant patients a significant decline in the daily average insulin dose was required to keep stable HbA1c after DAAs therapy (55.3 vs. 38.2 U/d; $p = 0.009$) (Teegen et al. 2019).

To be noticed, however, that a consistent number of studies did not show a long-term persistence in glycemic control, or showed no significant decline in HbA1c, or no effect of DAA treatment in patients with a severe CHC, or no effect at all, or an increase in TC and LDL values. A retrospective study by Weidner and colleagues showed that HCV eradication through DAA treatment was associated to with a significant reduction in fasting plasma glucose level and in the rate of patients with impaired fasting plasma glucose. In some CHC patients, however, the reduction of FPG levels was only transitory and no significant improvement in glycemic values was observed in cirrhotic patients up to 12 months after therapy (Weidner et al. 2018). In a retrospective study on 122 diabetic subjects with HCV infection published in 2019, Gilad et al. reported favorable HbA1c changes after DAA treatment in 42 (34%) of the 122; among these 42, only 20 of the 28 (71%) with available follow-up showed this effect sustained over 1.5 year (Gilad et al. 2019). Chaudury et al. prospectively examined for a median period of 28 months 251 HCV CHC patients, of whom 31% with HIV coinfection, before and after DAA therapy and only minimal changes in HbA1c and glucose were observed, independently of the achievement of SVR, HIV status, diabetes, or stage of liver disease. To be noticed that TC and LDL increased significantly after treatment (Chaudhury et al. 2017). Beig et al. performed a retrospective single-center study on 91 HCV-related liver transplant recipients with recurrent HCV infection who received DAA treatment, of whom 87 (96%) reached HCV eradication. HCV clearance was associated with a reduction in treatment doses for diabetes by 38% and from a decline of HbA1c levels from 35.5 ± 4.3 to 33.3 ± 3.6 mmol/mol 44 weeks post-treatment ($p = 0.03$); however, TC and LDL levels significantly increased posttreatment (Beig et al. 2018).

Some studies evaluated the changes in the incidence of T2DM after effective antiviral therapy. Butt and colleagues analyzed the data from patients of the U.S. Veterans Administration and recorded a more significant reduction in T2DM incidence rate in patients treated with DAAs: the incidence rates per 1000 person-years were 9.89 (95% confidence interval [CI] = 8.7–11.1) in DAA-treated patients, 19.8 (95% CI = 18.3–21.4) in those treated with pegylated interferon (Peg-IFN)/ ribavirin (RBV) treatment and 20.6 (95% CI = 19.6–21.6) in those left untreated ($p < 0.001$) (Butt et al. 2019). A cohort of 5127 nondiabetic patients treated with DAAs was analyzed by Li and coworkers; during an average follow up of 3.7 years they recorded an incidence of T2DM of 6.2% in the SVR group and of 21.7% in the non-SVR group (HR = 0.79; 95% CI = 0.65–0.96) (Li et al. 2019). Similarly, El Serag and colleagues analyzed 45,260 patients treated with DAAs, but the incidence of DM between the SVR and the non-SVR group did not significantly differ (21.04/1000 patients per year versus 23.11/1000 patients per year; hazard ratio (HR) = 0.98, 95% CI = 0.81–1.19, $p = 0.86$) (El Serag et al. 2019).

Concluding on this topic, there is still some disputes and the available data do not allow us to conclude on whether the achievement of SVR induces a persistent reduction in fasting glucose and HbA1c; despite this, the data from most studies strongly indicate good compensation of T2DM in HCV patients treated with DAA. Long-term prospective follow-up studies on the evolution of glycolic metabolism of diabetic and non-diabetic HCV patients who achieved SVR with DAA treatment are still needed to resolve the remaining disputes.

5 DAAs and Lipid Homeostasis

HCV infection has been associated with lipid and lipoprotein metabolism disorders, such as hypobetalipoproteinemia, hypocholesterolemia, and hepatic steatosis (Felmlee et al. 2013). HCV production is dependent on the very-low-density lipoprotein (VLDL) biosynthetic pathway, and circulating virions are associated with VLDL in lipoviral particles containing host apolipoproteins (APOs), including APOB, APOE, and APOC3 (Dai et al. 2008); the interaction between HCV virions, VLDL and low-density lipoprotein (LDL) particles is responsible for increased viral infectivity. In addition, HCV infection activates the sterol-regulatory-element-binding-protein (SREBP) 1c, which is involved in lipogenesis and HCV-related liver steatosis, partially due to ß mitochondrial-oxidation (Nielsen et al. 2006; Waris et al. 2007; Merz et al. 2011). It has also been shown that HCV core protein inhibits the activity of microsomal triglyceride transfer protein (MTP), resulting in liver steatosis and hypolipidemia. Because of the mechanisms mentioned above, spontaneous or treatment-related HCV eradication, down-regulating SREBP 1c and up-regulating both MTP and CPT-1 may reduce liver lipogenesis and increase VLDL secretion. Other data on lipid homeostasis in anti-HCV treatment is shown in Table 2. Eradication of HCV infection with IFN-based treatment has been found associated with normalization of hypolipidemia (Tada et al. 2009) and with an increased risk of cardiovascular events. HCV eradication has also been found associated with a decrease in CAP and LDL-C values, the parameter used as a measure of liver steatosis, which, however, correlates with elevated values of small-dense LDL-C (sdLDL-C), which has been shown to predict atherogenesis and dyslipidemia in patients with SVR24 (Kawagishi et al. 2018).

A rapid increase in serum LDL-C and total cholesterol (CT) values from the baseline to the 28th week of DAA treatment has also been described, the hyper lipid effect being stronger with ledipasvir/sofosbuvir than with daclatasvir/asunaprevir combination (Hashimoto et al. 2016). These Authors also observed a close correlation between the decrease in the HCV core antigen serum titers and the increase in LDL-L values, especially in patients treated with sofosbuvir + ledipasvir, suggesting a direct influence of the HCV clearance on serum cholesterol levels (Hashimoto et al. 2016).

In a prospective multicenter study on HCV infected and HIV-HCV coinfected patients treated with several DAA combinations, a significant increase in LDL cholesterol serum values was observed (Mauss et al. 2017), while HDL cholesterol remained stable. However, contrasting data were reported by Carvalho et al. (2018) who evaluated lipid homeostasis in chronically HCV-infected patients at baseline and 1 year after the achievement of SVR in 105 patients treated with sofosbuvir + ledipasvir ± RBV and 73 with IFN ± RBV: they found a significant increase in TC and LDL levels after treatment with both regimens, while serum triglyceride levels decreased only in the DAA group ($p = 0.015$) (Carvalho et al. 2018).

Another marker of lipid homeostasis is the ApoB/ApoA1 ratio, a better predictor of cardiovascular diseases than LDL alone: ApoB is the best direct marker of low atherogenic density LDL-19 and ApoA1 provides a good estimate of HDL. An Italian real-life study (Gitto et al. 2018) analyzed the metabolic changes in 100 HCV patients during a 24-week follow-up period after DAA treatment discontinuation and observed a significant reduction in ApoA1 blood levels and an increase in the ApoB/ApoA1 ratio and Lp (a) (Gitto et al. 2018). Supporting evidence is given by Younossi et al. who evaluated lipoproteins in genotype-1 patients who achieved SVR after ledipasvir/sofosbuvir ± RBV treatment, with an increase in ApoB and LDL and a decline in ApoA1 and apolipoprotein (Younossi et al. 2015).

Concluding on this point, the effect of DAA regimens, especially the sofosbuvir-based, on lipidic homeostasis is characterized by an increase in TC, LDL and the ApoB/ApoA1

Table 2 Changes in lipid homeostasis in DAA treated CHC patients

References	Study type	Number of patients, setting	Treatment	Results
Younossi et al. (2015)	International multicenter randomized open labelled study	100 CHC patients	50 patients received a 12-week LDV/SOF treatment and 50 a 12-week LDV/SOF + RBV treatment	Increase in ApoB and LDL and decline in ApoA1 and apolipoprotein serum values.
Hashimoto et al. (2016)	Retrospective study	100 CHC patients	DCV/ASV LDV/SOF	Higher increase in serum LDL-C and TC with LDV/SOF than with DCV/ASV; decrease in HCV-core antigenemia correlated with increase in LDL-C, mainly with LDV/SOF.
Mauss et al. (2017)	Prospective multicentre cohort study	520 CHC patients with or without HIV coinfection	SOF/PEG-IFN/RBV SOF/RBV SOF/DCV ± RBV SOF/SMV ± RBV SOF/LDV ± RBV OMV/PTV/r ± RBV OMV/PTV/r/DBV ± RBV	Significant persistent increase in TC and LDL-C with SOF/PEG-IFN regimen; triglycerides increased with SOF/PEG-IFN/RBV.
Younossi et al. (2016)	Retrospective study	127 CHC patients HCV-G2/3	SOF/RBV	Treatment restores distal sterol metabolites and increases TC.
Gitto et al. (2018)	Cohort study	100 CHC patients	SOF ± RBV 20 SOF/LPV ± RBV SOF/DCV ± RBV SOF/SMV ± RBV OMV/PTV/r + DSV ± RBV OMV/PTV/r ± RBV	Patients achieving SVR showed a strong decrease in ApoA1 levels and an increase in ApoB/ApoA1 ratio and in Lp(a)
Kawagishi et al. (2018)	Retrospective study	117 CHC patients	DCV/ASV SOF/LDV SOF/RBV OBV/PTV/r	Decrease in CAP and LDL-C in patients with high baseline values; elevated LDL-C and sdLDL-C in patients with liver steatosis and dyslipidaemia at SVR24.
Carvalho et al. (2018)	Prospective study	178 CHC patients	PEG±RBV SOF/LDV ± RBV	Increase in TC and LDL-C in both regimens; decrease in TG during DAA treatment.
Alessio et al. (2020)	Multicenter real-life study	243 HIV/HCV coinfected patients	DAA	Increase in TC and LDL-C serum level after 12 weeks of treatment.

CHC Chronic Hepatitis (Some cirrhotic cases are included), *SVR* sustained viral response, *LDL* low density lipoprotein, *CAP* controlled attenuation parameter, *sdLDL-C* small-dense low density lipoprotein cholesterol, *TC* total cholesterol, *ApoA1* apolipoprotein A1, *ApoB* apolipoprotein B, *Lp(a)* lipoprotein a, *DCV* daclatasvir, *IFN* interferon, *Peg-IFN* pegylated-interferon, *RBV* ribavirin, *TVR* telaprevir, *BOC* boceprevir, *OMV* ombitasvir, *PTV* paritaprevi, *r* ritonavir, *DSV* dasabuvir, *G/P* glecaprevir/pibrentasvir, *SOF* sofosbuvir, *SIM* simeprevir, *LDV* ledipasvir, *DCV* daclatasvir, *ASV* asunaprevir, *EBR* elbasvir, *GZR* grazoprevir, *VEL* velpatasvir, *cIMT* carotid intima-media thickness, *PWV* pulse-wave velocity, *T2DM* type 2 diabetes mellitus, *LDL* low-density lipoproteins, *HDL* high-density lipoproteins, *sdLDL* small dense lipoproteins

ratio. As a consequence of this, a higher incidence of cardiovascular events could have been expected after HCV eradication, eventuality not occurred probably because the adverse effect possibly induced by this increase could have been balanced or overcame by the favorable effect of the DAA-induced HCV eradication on cardiovascular system.

6 DAAs and Cardiovascular Diseases

HCV infection has also been described as an independent non-traditional risk factor for cardiovascular (CV) diseases (Domont and Cacoub 2016) since it induces an increased overall CV mortality (Goossens and Negro 2017; Cacoub et al. 2018a, b), a dysmetabolic syndrome (Loria et al. 2014) and a cytokine remodeling towards chronic systemic inflammation, which triggers endothelial dysfunction in response to recombinant HCV envelope protein (Urbaczek et al. 2014; Katsi et al. 2015; Gonzalez-Reimers et al. 2016; Cammarota et al. 2019; Sigon et al. 2019). Other mechanisms responsible for CV diseases in HCV patients have been identified in the procoagulant imbalance and IR/T2DM, which may directly cause vascular and cardiac damage (Domont and Cacoub 2016; Vassalle et al. 2018; Petta et al. 2018). Apart from some indirect mechanisms, HCV has also been proven to be a direct cardiotropic virus and a causative agent in structural cardiomyopathies, such as dilated, hypertrophic, right ventricular arrhythmogenicity (Matsumori et al. 1998; Matsumori 2006) and an inducer of cardiac fibrosis (Pepe et al. 2015) and myocarditis (Okabe et al. 1997; Goossens and Negro 2017) rarely secondarily to mixed cryoglobulinemia (Terrier et al. 2013). HCV-core protein elicits immune-mediated oxidative damage in myocardial tissue (Sanchez and Bergasa 2008; Frustaci et al. 2002), where HCV-RNA is also detectable (Matsumori et al. 1996; Okabe et al. 1997; Matsumori 2006). Also, genetic HLA and non-HLA susceptibility correlated to cardiomyopathy development has been described (Sanchez and Bergasa 2008). In addition, myocardial scintigraphy showed increased perfusion defects in 87% of 217 HCV-positive patients (Maruyama et al. 2013). This evidence has determined a partial shift in the practical interpretation of cardiovascular dysfunction in the management of HCV patients, CV disease increasingly representing a reason for prompt treatment, rather than an exclusion criterion.

Epidemiological studies showed an association between carotid atherosclerosis (Tomiyama et al. 2003; Perticone et al. 2015), carotid intima-media thickness (cIMT) and β-stiffness (Novo et al. 2018; Negro 2014) and the circulating of HCV-core protein (Ishizaka et al. 2003). However, the role of HCV in atherogenesis is still unclear as HCV might only be a "bystander" when detected within atherosclerotic plaques, rather than their cause (Goossens and Negro 2017; Vassalle et al. 2018; Romano et al. 2018), and the HCV-induced protective lipid profile constitutes a confounding factor on this point (Maggi et al. 1996; Oliveira et al. 2013; Novo et al. 2018). (Table 3).

Other studies reported an increased risk of acute coronary syndrome (ACS) (Tsai et al. 2015) and acute myocardial infarction (AMI) (Butt et al. 2017; Vassalle et al. 2018), with an association between the number of affected vessels and HCV viral load (Vassalle et al. 2004, 2018). Left ventricular dysfunction and congestive heart failure (CHF) may also occur, events predictable by N-terminal-pro-natriuretic peptide plasma values (NT-pro-BNP) (Vassalle et al. 2018). The hepatic damage (necroinflammation, steatosis and fibrosis) appears to promote T2DM and CV diseases in HCV patients (Lonardo et al. 2016). The "Heart and Soul" study analyzed 981 patients with CV diseases, of whom 8.6% was HCV-infected. The latter showed increased TNF-α levels and an augmented risk of heart failure and death (Tsui et al. 2009). The NHANES cohort examined 16,668 HCV patients and showed that CHC is an independent risk factor for impaired glucose metabolism (IR/T2DM), hypertension and congestive heart failure (Katsi et al. 2015). (Table 3).

HCV eradication has been associated with an improvement in CV and metabolic syndromes, creating a reduction in all-cause mortality both in patients receiving IFN-based therapy and in those treated with DAA (Goossens and Negro 2017; Adinolfi et al. 2018c; Mohanty et al. 2019; Revuelto Artigas et al. 2019b).

In the prospective CirVir cohort, including 878 HCV cirrhotic patients from 35 clinical centers, the achievement of SVR by IFN-based

Table 3 Impact of DAA therapy on cardiovascular disease

References	Study type	Number of patients, Setting	Treatment	Results, suggestions
Nahon et al. (2017)	Prospective cohort study	1,323 CHC patients	Peg-IFN/ RBV Peg-IFN/ RBV/TVR Peg-IFN/ RBV/BOC	SVR obtained in nearly half of the patients, associated with a lower risk of CV events.
Cacoub et al. (2018a, b)	Prospective cohort study	878 CHC patients	Peg-IFN/ RBV Peg-IFN/ RBV/TVR Peg-IFN/ RBV/BOC	SVR obtained in nearly half of the patients, associated with a reduced rate of CV events; Asian ethnicity, smoking, arterial hypertension, 2TDM and low serum albumin were identified as independent predictors of CV events.
Mehta et al. (2017)	Post-hoc analysis on a phase 3 trial	5,963 CHC HCV-G-1 patients; only those with basal glucose and TC values obtained in a fasting state were included	OMV/PTV/r/ DSV ± RBV	Significant reduction in serum triglycerides and glucose; reduced rate of CV events, particularly in patients with altered baseline biomarkers.
Tran et al. (2018)	Post-hoc analysis on phase 3 trial	1,554 CHC patients	G/P	Significant improvement in biomarkers predictive of extrahepatic diseases, including CV diseases and metabolic syndromes.
Petta et al. (2018)	Prospective cohort study	182 child-Pugh A cirrhotic patients	SOF/RBV SOF/ SIM ± RBV SOF/ LDV ± RBV SOF/ DSV ± RBV OMV/PTV/r/ DSV ± RBV	SVR resulted in amelioration of carotid atherosclerosis, evaluated by US measuring of cIMT; such amelioration was not observed in obese subjects.
Butt et al. (2018)	Cohort study	242,680 veterans with CHC with no history of CV disease	Peg-IFN/ RBV Peg-IFN/ RBV/BOC Peg-IFN/ RBV/TPV SOF/ SIM ± RBV SOF/ DCV ± RBV LDV/ SOF ± RBV PTV/r/OMV/ DSV ± RBV EBR/ GZR ± RBV SOF/VEL	SVR resulted in a lower risk of CV events compared with controls pair matched by age, race, sex, and baseline values.
Novo et al. (2018)	Observational cohort study	39 HCV Child-Pugh A cirrhotic patients	SOF/RBV SIM/SOF/ RBV SOF/ LDV ± RBV SOF/DSV/	SVR resulted in a significant amelioration of subclinical CV alterations (evaluated by cIMT, PWV, β-stiffness, global longitudinal strain); reduction of

(continued)

Table 3 (continued)

References	Study type	Number of patients, Setting	Treatment	Results, suggestions
			RBV OMV/PTV/r/ DSV ± RBV	systemic inflammation, particularly in T2DM patients.
Revuelto Artigas et al. (2019a, b)	Observational prospective study	85 CHC patients without T2DM, kidney disease, nor CV diseases, of whom 38.8% non-responders to previous PEG-IFN/RBV treatment	SOF ± RBV SOF/ LDV ± RBV SOF/ SIM ± RBV SOF/ DCV ± RBV OMV/PTV/r/ DSV ± RBV	HCV clearance wasn't followed by cIMT improvement; worsening in blood lipid composition was observed 1 year after treatment. Mid-term effects should be carefully evaluated.
Ichikawa et al. (2019)	Observational prospective study	48 CHC patients	SOF/RBV SOF/LDV DCV/ASV	An increase in cIMT and unfavourable lipidic profiles were observed 1 year after SVR, suggesting the need for long-term follow up studies for a conclusive statement.

CHC Chronic Hepatitis (Some cirrhotic cases are included), *SVR* sustained viral response, *CV* cardiovascular, *IFN* interferon, *Peg-IFN* pegylated-interferon, *RBV* ribavirin, *TVR* telaprevir, *BOC* boceprevir, *MACE* major adverse cardiovascular events, *HIV* human immunodeficiency virus, *HBV* hepatitis B virus, *OMV* ombitasvir, *PTV* paritaprevi, *r* ritonavir, *DSV* dasabuvir, *G/P* glecaprevir/pibrentasvir, *SOF* sofosbuvir, *SIM* simeprevir, *LDV* ledipasvir, *DCV* daclatasvir, *ASV* asunaprevir, *EBR* elbasvir, *GZR* grazoprevir, *VEL* velpatasvir, *cIMT* carotid intima-media thickness, *PWV* pulse-wave velocity, *T2DM* type 2 diabetes mellitus, *LDL* low-density lipoproteins, *HDL* high-density lipoproteins, *sdLDL* small dense lipoproteins

regimens was associated with a decrease in CV mortality (Cacoub et al. 2018b). In 2018, Tran et al. studied a cohort of 1554 HCV patients with CHC without cirrhosis enrolled in two phase-3 clinical trials to evaluate the tolerability and efficacy of glecaprevir/pibrentasvir combination therapy and found a statistically significant reduction in CV diseases and in metabolic syndromes in those who achieved SVR (Tran et al. 2018); a post-hoc analysis on 5963 HCV patients undergoing ombitasvir/paritaprevir/ritonavir/dasabuvir+RBV combination therapy obtained similar results (Mehta et al. 2017). Thirty-nine Italian HCV-cirrhotic patients showed no major CV adverse events following HCV eradication with different DAAs regimens and a decrease in subclinical cardiovascular alterations as detected by PWV and β-stiffness index (Novo et al. 2018).

Butt et al. investigated the risk of CV events in USA veterans with CHC, 4436 treated with Peg-IFN and 12,667 with DAAs, matched with untreated controls according to potential confounding factors: CV events were observed in 7.2% of treated patients and in 13.8% of controls, indicating a significantly lower risk after SVR achievement (Butt et al. 2018). An Italian study on 182 HCV patients with severe liver fibrosis and SVR to DAA evaluated the dynamics of carotid atherosclerosis by measuring the carotid intima-media thickness (cIMT): there was a significant decrease in cIMT during a long-term post-treatment follow-up (from 0.94 ± 0.29 mm at the baseline to 0.81 ± 0.27 at the end of observation, $p < 0.001$) and a reduction of the number of patients with an increased carotid thickening (from 42.8 to 17%, $p < 0.001$) (Petta et al. 2018). Instead, a Spanish prospective study on 85 HCV-cirrhotic patients did not find cIMT reduction within the 12th month after DAA-mediated HCV eradication (Revuelto Artigas et al. 2019a). In addition, Ichikawa et al. analyzed 48 CHC patients 1 year after they achieved SVR to DAA treatment and observed an increase of cIMT associated with an unfavorable lipidic profile (increase in LDL, HDL, sdLDL) (Ichikawa et al. 2019), suggesting that we cannot conclude on this point and further

studies are required to untangle the remaining controversies (Osibogun et al. 2017). Concluding on this point, despite some undesirable effects eventually due to the increase in Total and LDL cholesterol, an overall evaluation of the available data suggests that HCV eradication with DAA therapy, by eliminating numerous other harmful effects of HCV, exerts a favorable action on cardiovascular system, which results in a reduction of adverse events and reduced mortality.

7 DAAs and Renal Function

HCV infection and chronic kidney diseases (CKD) are joined by two main links, the first being the frequent exposure to HCV of patients with advanced CKD in dialysis units, and the second that HCV infection is able to directly induce kidney disease. Epidemiological investigations have underlined that HCV chronic infection increases the incidence of CKD and accelerates CKD progression to end-stage renal disease (Henson and Sise 2019). A strong correlation between anti-HCV positivity and the incidence of CKD has been demonstrated in a meta-analysis published in 2017 (Fabrizi et al. 2017), where anti-HCV positivity was identified as an independent predictor of death for dialysis patients (Fabrizi et al. 2020). HCV infection may contribute to tissue damage by directly infecting the endothelium, tubular epithelial cells, renal infiltrating leukocytes and other types of renal cells, such as mesangial cells, and is associated with three different kidney lesions: mixed cryoglobulinemic nephropathy, membranous-proliferative glomerulonephritis and membranous nephropathy.

Interferon-based treatment induced HCV eradication in nearly half of the treated patients, an event associated with a decreased rate of patients with renal disease and with a reduced progression to an end-stage renal disease (Arase et al. 2011; Feng et al. 2012; Hsu et al. 2015a; Montero et al. 2018; Fabrizi et al. 2020).

With the introduction of DAA therapies for chronic hepatitis C, the SVR rate also increased significantly in patients with CKD (Perazzo et al. 2020). A meta-analysis evaluating 11 studies on HCV patients with CKD-4/5 and treated with DAA-based therapy showed an SVR12 rate of 93.2%, an incidence of serious adverse events of 12.1% and treatment withdrawal of 2.2%, suggesting that DAA-based therapy is safe and efficient in eradicating HCV infection even in this patient setting (Li et al. 2017). It has also been shown that DAA therapy reduces the risk of kidney disease in CHC patients (Fabrizi et al. 2020).

The favorable effect of DAA treatments on glomerular filtration rate (eGFR) has also been proven, especially in patients with mild or moderate CKD (Calleja et al. 2017; Coppola et al. 2019; Sise et al. 2020; D'Ambrosio et al. 2020) (Table 4). In a cohort of 3,264 patients (9.5% in stage CKD 3 and 0.7% in stage 4/5) eGFR improved more significantly in those in CKD-3a stage ($p < 0.0001$) and CKD-3b ($p = 0.0007$) than in those in stage CKD-4/5 ($p = 0.024$) (D'Ambrosio et al. 2020). Half of 38 Spanish patients with baseline eGFR <60 ml/min/1.73 m^2 showed a remarkable improvement in these values after HCV eradication with DAA treatment (Calleja et al. 2017). Sise et al. in a follow-up of 573 days (SD = 337) after the discontinuation of DAA observed in patients with baseline eGFR <60 ml/min 1.73 m^2 the persistence of a substantial improvement induced by DAA treatment (Sise et al. 2020).

Instead, the results may be different if sofosbuvir-based regimens are used, as observed by Shin et al. in 4 of 28 patients with stage 3 CKD who showed a reduction of eGFR of more than 30% (Shin et al. 2017) (Table 4). In addition, in a cohort of 3264 patients, of whom 89.8% had baseline eGFR >60 ml/min, this index significantly decreased in those with CKD-1 ($p < 0.0001$) and CKD-2 ($p = 0.0002$) under a sofosbuvir- RBV combination treatment (D'Ambrosio et al. 2020). Similar results were found in a Spanish cohort of 1567 patients treated with ombisartan/paritaprenvir/ ritonavir + dasabuvir ± RBV and in 1,758 treated with ledipasvir/sofosbuvir ± RBV, where a mean eGFR reduction of −1.6 (SD = 12.4) ml/min/1.73 m^2 was observed in patients with baseline normal renal function (Calleja et al. 2017). In a

Table 4 Studies on the impact of DAA regimens on renal function

References	Study type	Number of patients, Setting	Treatment	Results, suggestions
Shin et al. (2017)	Observational study	28 CHC-G 1 patients with eGFR 30–60 ml/min	SOF/PEG/RBV SOF/SIM SOF/LDV	Worsening in renal function may occur; careful monitoring is suggested.
Calleja et al. (2017)	Cohort study	3,325 CHC-G 1 patients in various CKD stages and with eGFR >90 ml/min	LDV/SOF ± RBV OMV/PTV/ r + DSV ± RBV	Post-treatment eGFR, available for only 659 patients; for those with normal baseline renal function the mean (SD) change in eGFR was −1.6 (12.4) mL/min/1.73 m^2
Butt et al. (2018)	Cohort study	17,624 CHC patients in various CKD stages and with eGFR >60 ml/min	SOF/LDV ± RBV OMB/PAR/r ± RBV	A decline in eGFR values and development of anaemia were observed in a substantial proportion of patients.
Álvarez-Ossorio et al. (2018)	International, prospective, multicohort study	1,131 CHC patients in various CKD stages and with eGFR >90 ml/min, with or without HIV infection.	SOF/SIM SOF/LDV SOF/DCV OMV/PTV/r ± DSV	eGFR slightly declined during treatment, an effect persisting up to 12 weeks after treatment, regardless of HIV status.
Soeiro et al. (2018)	Observational prospective study	333 CHC patients with HIV coinfection, in various CKD stages and with eGFR >90 ml/min.	SOF/LDV ± RBV	Decrease in eGFR during treatment, reversible after treatment discontinuation.
Taramasso et al. (2018)	Observational prospective study	213 CHC-G 1 patients with HIV coinfection, in CKD stages 1, 2 or 3.	OMV/PTV/r/DSV	eGFR significantly declined during treatment, an effect reversed during a prolonged post-treatment follow-up.
Coppola et al. (2019)	Cohort study	403 CHC patients in various CKD stages and with eGFR >90 ml/min	SOF/RBV SOF/SIM ± RBV OMB/PAR/r ± RBV SOF/LDV ± RBV SOF/DCV ± RBV	Improvement in renal function.
Sise et al. (2020)	Cohort study	2,319 CHC patients in various CKD stages and with eGFR >90 ml/min	INF-containing regimens SOF-based regimens RBV-containing regimens	Treatment slowed CKD progression.
D'Ambrosio et al. (2020)	Observational study	3,264 CHC patients in various CKD stages and with eGFR >90 ml/min	SOF-based and no-SOF-based±RBV	eGFR declined during treatment in patients with preserved renal function and improved in those with CKD; no reversion upon drug discontinuation.

CHC Chronic Hepatitis (Some cirrhotic cases are included), *SVR* sustained viral response, *CKD* chronic kidney disease, *IFN* interferon, *Peg-IFN* pegylated-interferon, *RBV* ribavirin, *TVR* telaprevir, *BOC* boceprevir, *HIV* human immunodeficiency virus, *HBV* hepatitis B virus, *OMV* ombitasvir, *PTV* paritaprevi, *r* ritonavir, *DSV* dasabuvir, *G/P* glecaprevir/pibrentasvir, *SOF* sofosbuvir, *SIM* simeprevir, *LDV* ledipasvir, *DCV* daclatasvir, *ASV* asunaprevir, *EBR* elbasvir, *GZR* grazoprevir, *VEL* velpatasvir, *T2DM* type 2 diabetes mellitus

cohort of 17,624 patients treated with sofosbuvir + ledipasvir ± RBV or with paritaprevir/ritonavir/ombitasvir ± RBV, Butt et al. observed that 30% and 38% of patients in the two different therapeutic regimens, respectively, showed a reduction in eGFR by at least 10 ml/min/1.73 m^2 compared to the baseline normal value. However, it is useful to underline that these possible reductions in eGFR generally disappear within 12 weeks from the suspension of therapy (Butt et al. 2018).

In a Spanish/Portuguese cohort of 1131 patients, including 658 (58%) HIV/HCV-coinfected patients, the eGFR slightly declined during DAA treatments in patients with normal to moderately impaired renal function (Álvarez-Ossorio et al. 2018). A similar decrease in eGFR was observed in 273 HIV/HCV coinfected patients, more pronounced in those receiving tenofovir, in those treated with DAA for 24 weeks ($p = 0.009$) and in cirrhotic patients ($p = 0.036$) (Álvarez-Ossorio et al. 2018). Similar results were observed in a study on 144 HIV/HCV coinfected patients; a strong eGFR decline was observed in those concomitantly treated with tenofovir ($p = 0.0001$), ribavirin (p = 0.0001) or integrase inhibitors ($p < 0.0001$), in those with a longer duration of HIV ($p = 0.0002$) or HCV infection ($p = 0.035$), in those with a lower baseline HCV RNA ($p < 0.0001$), or with a previous HCV treatment ($p < 0.0001$), and in the elderly ($p < 0.0001$) (Taramasso et al. 2018).

In conclusion on this point, the HCV eradication obtained with DAA therapy in CHC patients exerts a beneficial effect even in those with impaired renal function and only some conflicting data persist on the effect of some DAA regimens on eGFR. Similar beneficial effects of DAA therapy are also observed in patients with HCV/HIV co-infection and even here doubts persist only on the use of drugs which may lead to a transient reduction in eGFR.

8 DAA Treatment of Cryoglobulinemia

Cryoglobulinemia is a condition characterized by the presence of cryoglobulins in the blood, which reversibly precipitate and form a gel at less than 37 °C and dissolve over 37 °C (Roccatello et al. 2018). Brouet's classification defines three types of cryoglobulinemia: Type I with single monoclonal immunoglobulins; type II, a mixed cryoglobulinemia with monoclonal and polyclonal immunoglobulins; Type III, a mixed cryoglobulinemia with IgM and IgG, both polyclonal. (Brouet 1983). Cryoglobulins could be detected in 25–30% of HCV-positive patients (Dammacco and Sansonno 2013) and 80–90% of cases with type II and type III mixed cryoglobulinemia carry HCV infection (Minopetrou et al. 2013; Roccatello et al. 2018) associated with a high incidence of severe liver fibrosis and cirrhosis (Roccatello et al. 2018). Arthralgia, asthenia and palpable purpura are the most common clinical manifestations of HCV related mixed cryoglobulinemic syndrome (MCS) and skin the most frequently organ involved; however, hematological disease and severe organ disfunction or failure (kidney, hearth, central nervous system, etc.) may occur (Dammacco and Sansonno 2013; Minopetrou et al. 2013). Treatment with Standard IFN provides HCV eradication in only a quarter of treated cases, with a substantial improvement in both liver function and CMS; in cases of temporary viral response, however, CMS usually relapses (Dammacco and Sansonno 2013). The introduction of treatment with Peg-IFN α-2a or 2b and RBV induced SVR in about half of treated patients. In a cohort study published by Gragnani et al. in 2015, the persistence of cryoglobulinemia was linked to a higher probability of Peg-IFN/RBV treatment failure (HR 2.03, 95% CI = 1.12–3.68, $p = 0.0204$), while the 63 HCV patients with MCS who reached SVR showed a clear improvement in clinical and laboratory MCS manifestation throughout a mean follow up period of 92.5 months (Gragnani et al. 2015).

The combination of a first generation DAA (telaprevir or boceprevir) with Peg-INF and RBV achieved HCV eradication in 65–75% of treated patients with remission or reduction of sign and symptoms of MCS (Humphries et al. 2014; Gragnani et al. 2014; Saadoun et al. 2014, 2015; Cornella et al. 2015).

IFN-based regimes have become obsolete once the second generation DAAs have been introduced, because of their good safety profile and higher effectiveness (SVR in 95% of treated patients). Same studies published in 2015 and in 2016 have shown a frequent remission of symptoms and signs of MCS in CHC patients after a DAA treatment (Makara et al. 2015;

Chak et al. 2015; Koga et al. 2017; Obata et al. 2017). Several cohort studies reported high percentages of patients who achieved a remarkable improvement of cryoglobulinemic vasculitis after HCV eradication with DAA therapy (Sise et al. 2016; Bonacci et al. 2017; Saadoun et al. 2017; Lauletta et al. 2017; Emery et al. 2017; Comarmond et al. 2017; Gragnani et al. 2018; Hassan et al. 2018; Miailhes et al. 2018; Pozzato et al. 2020) (Table 5); our meta-prop analysis on these percentages, shows an overall improvement in 78% of patients (95% CI: 0.69–0.86 p = < 0.001) (Fig. 1). A cohort study by Mahale et al. detected the incidence rate (*IR*) per 1,000 persons-year (Py) of CMS in HCV positive patients, either never treated (*IR* 1000 Py = 0.72; 95% CI = 0.66–0.78), or DAA-treated without SVR (*IR* 1000 Py =0.52; 95%CI = 0.41–0.67), or DAA-treated with SVR (*IR* 1000 Py =0.33; 95%CI: 0.21–0.5), showing that HCV RNA clearance is a protective factor in this setting; the adjusted hazard ratios (aHR) indicate no significant difference between treated patients without SVR vs. untreated, aHR 1.11, (95% CI = 0.85–1.45), whereas the differences between patients who reached SVR versus untreated and versus those treated without SVR ware both statistically significant, respectively 0.61 (95% CI = 0.39–0.94) and 0.55 (95% CI = 0.33–0.90) (Mahale et al. 2018). Cacoub et al. analyzed the effect of DAA-induced SVR obtained on HCV extrahepatic manifestations in a meta-analysis including 16 studies; the achievement of SVR was associated with a reduction in extrahepatic mortality (OR 0.44; 95% CI = 0.28–0.67), a higher complete remissions of clinical signs and symptoms of cryoglobulinemic vasculitis (OR 20.76; CI = 6.73–64.05) and with a greater efficacy in malignant B-cell lymphoproliferative diseases (OR 6.49; CI = 2.02–20.85) (Cacoub et al. 2018a).

Out of 12,985 HCV genotype 4 CHC patients successfully treated with second generation DAAs, Fayed et al. identified 50 patients with de novo detectable serum cryoglobulins and vascular renal affection 4.3 ± 1.3 months after treatment, the most common type of kidney affection observed in renal biopsies being membranoproliferative glomerulonephritis (52%); chronic kidney disease (CKD) developed in 46% of cases. The Authors concluded that de novo cryoglobulinemic glomerulonephritis and progression to CKD rarely complicate a successful DAA treatment (Fayed et al. 2018).

Concluding on this point, DAA treatment finds full application in CHC patients with MCS, since it has a good safety profile, induces HCV eradication in nearly 95% of patients and is associated with remissions of cryoglobulinemic vasculitis and with a reduction extrahepatic mortality. In addition, MCS infrequently occurs in CHC patients after HCV eradication.

9 DAAs and Lymphoma

Strongly characterized as a hepatotropic virus, HCV also infect and replicate within B and T cells (Sarhan et al. 2018) and is capable of driving clonal expansion of B lymphocytes (Kasama et al. 2011) within the complex HCV syndrome; therefore, HCV infection is associated and causally related to lymphomagenesis (Zignego et al. 1997). Worthy of notice, patients with HCV-driven type II mixed cryoglobulinemia are at increased risk for NHL (with a 35-fold higher risk than the general population) (Defrancesco et al. 2020). A vast study by the International Lymphoma Epidemiology Consortium and other epidemiologic studies have identified an association between chronic HCV infection and B-NHL subtypes, particularly with the diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma) (Suarez et al. 2006; De Sanjose et al. 2008; Rattotti et al. 2019; Defrancesco et al. 2020). The double tropism and the double oncogenic potential of HCV is also underlined by some reports on HCV infected patients with both HCC and lymphoma (Shapira et al. 2001; Utsunomiya et al. 2009; Becker et al. 2010).

The first evidences for a link between HCV infection and lymphoma date back to the 1990s (Ferri et al. 1994; Pioltelli et al. 1996; Hanley et al. 1996; Galli et al. 1996; Brind et al. 1996;

Table 5 Impact of DAAs treatment on clinical manifestation of cryoglobulinemic vasculitis

References	Study type	Number of patients	Treatment	Improvement of symptoms related to cryoglobulinemia (complete or partial improvement) (n° pts)
Sise et al. (2016)	Cohort	12	SOF/SIM, SOF/RBV	8 among 12 symptomatic.
Bonacci et al. (2017)	Cohort	64	3D, SOF/LDV, SOF/SIM, SIM/DCV, SOF/DCV, Peg-IFN/RBV/DAAs, GRZ/ELB, FAL/DEL	30 patients among 32 symptomatic.
Saadoun et al. (2017)	Cohort	41	SOF/DCV	37 among 41 symptomatic.
Lauletta et al. (2017)	Cohort	22	SOF/RBV, 3D ± RBV, SOF/LDV, SOF/DCV	16 among 22 symptomatic.
Emery et al. (2017)	Cohort	83	PegIFN/RBV/ TEL or BOC, SOF/SIM, SOF/RBV, SOF/LDV, 3D ± RBV	11 among 18 symptomatic.
Comarmond et al. (2017)	Cohort	27	SOF ± RBV, SOF/DCV, SOF/SIM	24 among 27 symptomatic.
Gragnani et al. (2018)	Cohort	139	3D ± RBV, SOF/DCV ± RBV, SOF/LDV ± RBV, SOF/SIM ± RBV, SOF/RBV	65 among 77 patients symptomatic with SVR.
Hassan et al. (2018)	Cohort	120 (63 with cryoglobulinemia)	SOF/DCV	55 among 63 patients with Meltzer's triad.
Miailhes et al. (2018)	Cohort	47	SOF/RBV, Peg-IFN/SOF/RBV, SOF/NS3/4 PI±RBV, SOF/NS5A inhibitors±RBV, 3D.	14 among 28 symptomatic patients.
Pozzato et al. (2020)	Cohort	67	3D, SOF/SIM, ASUNEPRAVIR/DCV, SOF/LDV ± RBV	40 among 67 symptomatic patients.

SOF sofosbuvir, *SIM* simeprevir, *3D* ombitasvir/paritaprevir/ritonavir/dasabuvir, *LDV* ledipasvir, *DCV* daclatasvir, *GRZ* grazoprevir, *PIB* pibrentasvir, *FAL* faldaprevir, *DEL* deleobuvir, *TEL* telaprevir, *BOC* boceprevir

Zignego et al. 1997), either in association or, more rarely, in the absence of mixed cryoglobulinemia (De Vita et al. 1997, Luppi et al. 1996). Subsequently, the aetiological hypothesis was enriched by the detection of HCV RNA in in NHL lesions lymphoma samples (Ohsawa et al. 1998; Karavattathayyil et al. 2000) and by the demonstration of a positive correlation between viral replication and the risk to develop lymphoma (Amiel et al. 2000). This link was confirmed by a Meta-analysis published in 2006 (Dal Maso et al. 2006) and by the data from the Swiss Cohort Study on HIV/HCV coinfected patients (Franceschi et al. 2006). In 2003, an Italian multicentre case-control study confirmed that B-NHL may originate in CHC patients, suggesting a significant potential benefit of an antiviral treatment in limiting the burden of HCV-related haematological disease (Mele et al. 2003). The association of HCV infection with NHL was further confirmed in a case control study which, however, failed to find a significant correlation with Hodgkin Disease (Montella et al. 2001). Zhou et al., in 2016, proposed the HCV load as a prognostic factor in patients with HCV-positive diffuse large B cells lymphoma. (Zhou et al. 2016); in 2017, Shimono proposed HCV infection as an independent factor in the prognosis of follicular lymphoma (Shimono et al. 2017), In 2019, a meta-analysis by Zhu et al. reaffirmed the prominent role of HCV as a risk factor for NHL. (Zhu et al. 2019) and more recently, in 2020, a Turkish multicentre cohort study proposed HCV as a causative and prognostic factor for splenic marginal zone lymphoma (Okay et al. 2020).

It is worth noticing that some studies have highlighting geographic variations for the HCV-NHL association, suggesting a deeper evaluation of HCV genotypes and cofactors

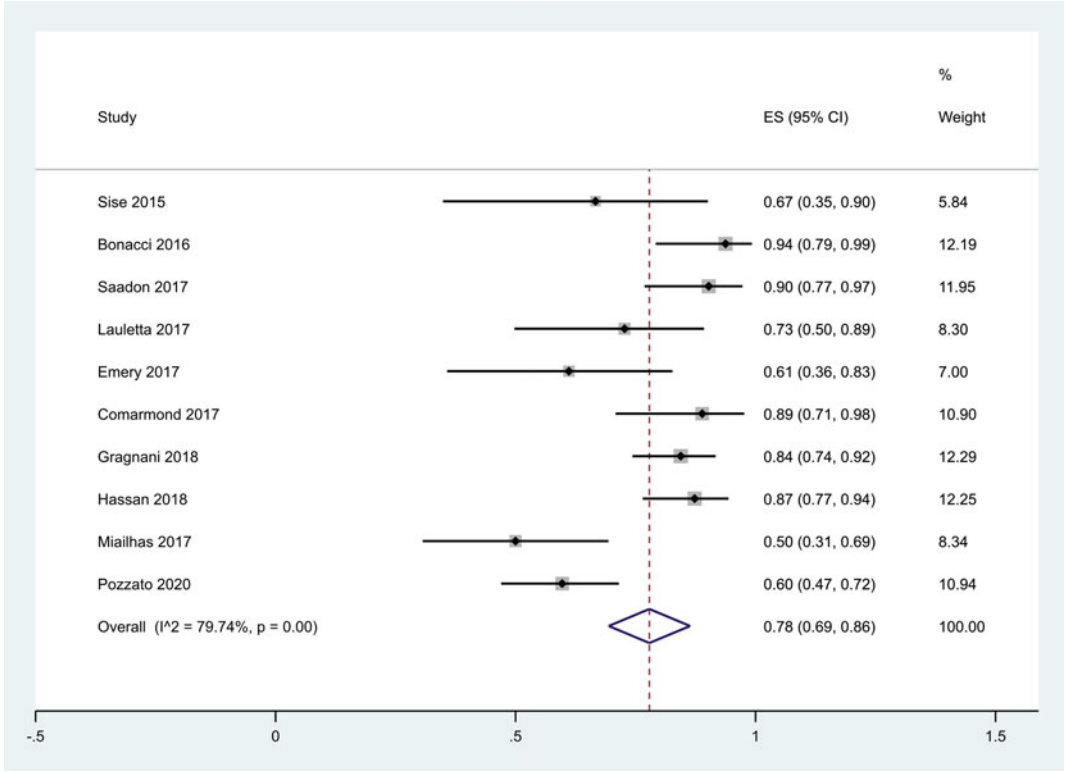

Fig. 1 The proportion of improvement considering clinical manifestation of cryoglobulinemic vasculitis after DAAs treatment and SVR

responsible of discrepancies. In detail, a meta-analysis found a strikingly positive association between HCV seropositivity and NHL only for Italian and Japanese patients (Matsuo et al. 2004); in the 2001 a prospective study on 1576 patients., concluded that HCV positivity was scarcely prevalent (1.83%) in patients with B-NHL in France (Hausfater et al. 2001).

It is worth reporting that a few other some studies denied the association between CHC and B-cell lymphoma (Collier et al. 1999; Avilés et al. 2003).

Considering the complex role of HCV in the related haematological disease the "Fondazione Italiana Linfomi" designed a specific "HCV prognostic score" to its management (Defrancesco et al. 2020).

Underlying mechanisms for HCV lymphomagenesis are far from being fully understood, but seem to revolve around chronic antigen-driven proliferation of B-cells, majorly mediated by viral proteins such as HCV core protein (Suarez et al. 2006; Alisi et al. 2007), and E2 envelope protein (Quinn et al. 2001; Douam et al. 2015), also observed in T cell lines (Zhao et al. 2006), with mechanisms promote a mutator phenotype of immunoglobulin and proto-oncogenes (e.g. Ig heavy chain, BCL-6, p53, and beta-catenin) (Machida et al. 2006a), increasing NF-κB expression and contrasting antiapoptotic functions (e.g. Bcl-2) (Defrancesco et al. 2020). Furthermore, HCV can upregulate B-cell receptor signalling (Dai et al. 2016) and trigger the enhancement of TLR4 expression along with IFN-beta and interleukin-6 production (Feldmann et al. 2006; Machida et al. 2006b). Additional mechanisms involve mitochondrial dysregulation and oxidative damage, with DNA damage, STAT3 activation (Machida et al. 2006a) and epigenetic alterations in microRNA (Peveling-

Oberhag et al. 2012), also in DLBCL (Augello et al. 2014). These complex mechanisms are extensively discussed in some dedicated reviews (Landau et al. 2007; Visco and Finotto 2014). A role in HCV lymphomagenesis has been proposed also for genetic risk factors, like the fibronectin gene polymorphisms (Fabris et al. 2008) and MHC II (e.g HLA-DQ) (De Re et al. 2004, 2009).

Of notice, HCV-related lymphoproliferative diseases present peculiar molecular signature, with possible therapeutic implications (De Re et al. 2012; Peveling-Oberhag et al. 2013; Visco et al. 2017), including an increase in specific oncogene expression, such as Bcl-2, correlated with t(14;18) translocation which disappears following HCV eradication (Zignego et al. 2000). A long past use of IFN in HCV positive patients with lymphoma was linked to the well-known antiproliferative effect of this drug, although toxicity was not negligible and SVR was far from being satisfactory, since HCV eradication was achieved by a quarter of patients receiving Standard IFN-based therapy by approximately 50% of those treated with Peg-IFN + RBV. The Peg-IFN and first-generation DAA-based therapy has been demonstrated able to obtain the SVR in 65–75% of HCV-1 CHC patients. A meta-analysis published by Peveling-Oberhag et al. in 2016 confirmed the strong association between SVR and B-NHL regression, particularly in MZL, suggesting that antiviral treatment may function as a first-line therapeutic approach when I-CT is not immediately required (Peveling-Oberhag et al. 2016), leading to a better overall survival in case of SVR (Hosry et al. 2016, Masarone and Persico 2019). Of notice, Su et al. observed a reduced risk for lymphoma development in patients who received early successful therapy for HCV infection (Su et al. 2019).

Some case-reports published in In 2015 showed that the second generation DAAs exert a favourable clinical effect on HCV lymphoma after HCV clearance: Rossotti et al. described a case of splenic MZL obtaining a favourable rapid hemato-virologic response after a 16-week treatment with faldaprevir, deleobuvir and RBV (Rossotti et al. 2015); Sultanik et al. reported the case of a HCV-positive woman with disseminated extranodal MZL treated with 4 weeks sofosbuvir + RBV, followed by 12 weeks sofosbuvir + daclatasvir, obtaining HCV clearance and a concomitant regression of lymphoma (Sultanik et al. 2015); Lim et al. reported a case of MZL regression by sofosbuvir + RBV (Lim et al. 2015); Carrier et al. reported a satisfactory viro-hematologic response (Carrier et al. 2015). in 5 NHL patients treated with sofosbuvir plus simprevir or daclatasvir, combined with chemotherapy one patient with DLBCL.

The French "ANRS HC-13 Lympho-C" Study observed two prospective cohorts of HCV-B-NHL patients: the first of 61 patients receiving Peg-IFN + RBV (combined with the first generation DAAs telaprevir or boceprevir only in some of them), and the second of 10 patients treated with sofosbuvir plus ledipasvir or simeprevir or daclatasvir or RBV; SVR led to a reduced risk for lymphoma progression, but IFN based regimen was poorly tolerated in DLBCL patients, already weakened by previous chemotherapy (Alric et al. 2016). A beneficial clinical effect of DAA therapy with ombitasvir/paritaprevir/RBV and dasabuvir was described in a HCV patient with aggressive double-hit B-cell lymphoma. (Galati et al. 2016).

In 2016, Arcaini et al. analysed a cohort of 46 patients with HCV-related lymphoproliferative disorders (indolent B-NHL, majorly MZL, and chronic lymphatic leukaemia, CLL): 39 subjects received sofosbuvir plus simprevir or RBV or daclatasvir or ledipasvir, while 7 subjects received an alternative regimen (paritaprevir/ ritonavir/ ombitasvir ± dasabuvir ± RBV or faldaprevir/ deleobuvir/ RBV); 98% of patients achieved SVR, while a hematologic response was obtained in 67% of cases (complete in 12 patients, 26%), more prominent in MZL, while no CLL/SLL patient obtained hematologic regression (Arcaini et al. 2016). Frigeni et al. observed a cohort of 100 patients with indolent HCV-B-NHL (only one with decompensated cirrhosis who failed to obtain SVR, with presenting lymphoma progression); 66 patients were treated with a DAA regimen and the remaining with an IFN-based regimen; nodal involvement was

apparently more severe and less responsive, cryoglobulinemia wasn't a relevant outcome modifier, the strongest responsiveness was observed in MZL and, noticeably, SVR (either ± IFN) led to an augmented overall hematologic response (Frigeni et al. 2020).

In 2019, a meta-analysis reaffirmed a powerful association between HCV eradication by DAA and favorable hematologic outcomes for HCV-positive B-NHL (Masarone and Persico 2019). Of notice, other studies observed a reduced risk for lymphoma development in patients who received early successful therapy for HCV infection (Su et al. 2019; Iwane et al. 2019) and prevention of relapse of DLBCL and, more generally, of malignant lymphoma (Pellicelli et al. 2018). As a complementary outcome, DAA eradication in HCV-positive DLBCL may reduce the liver toxicity of immune-chemotherapy (I-CT), and it can be offered after or even during I-CT, with the advantage of a timely management (Occhipinti et al. 2018; Merli et al. 2019, 2020).

Although the favourable effect of HCV eradication on the course of lymphoproliferative diseases is evident, some limitations have been underlined. For example, Schiavinato et al. analysed the peripheral blood lymphocytes populations and Ig light chain κ/λ ratio variations as indicators for monoclonal B-cell response in 9 patients with CHC and lymphoproliferative disorders treated with Ombitasvir/Paritaprevir/Ritornavir/Dasabuvir plus RBV; although all patients reached SVR12 and a global reduction of B cells, they still presented monoclonal components (Schiavinato et al. 2017). Rodríguez de Santiago et al. warned the scientific community against an excessive optimism as 6 patients out of 9 HCV patients with a lymphoproliferative disease presented a persistence of monoclonal B lymphocytes in the bone marrow 1 year after SVR; in addition, two NHL patients required additional therapy (chemotherapy and/or immunotherapy) after SVR was achieved (Rodríguez de Santiago et al. 2018). Furthermore, in aggressive B-cells lymphoma, such as DLBCL, there is a limited evidence for the therapeutic aid by DAA (Visco amd Finotto 2014).

In conclusion, available evidence increasingly recognizes the beneficial role of HCV eradication in the treatment of HCV-related lymphoproliferative disorders, particularly obtained with the highly tolerable and effective IFN-free DAA-based regimens, evidence reinforcing the importance of HCV in lymphomagenesis. Antiviral therapy appears majorly important in patients with indolent NHL, but some recent information support the use of HCV eradication also in patients affected by the more aggressive HVC-positive DLBCL, even if further investigation is needed in this topic.

10 Conclusion

In the last decade, emphasis has been placed on the extrahepatic involvement of chronic HCV infection, now fully recognized as a systemic disease, having reversed the previous "liver-focused" holistic paradigm towards an HCV pleiotropic action. In addition to being hepatotropic, HCV is also a lymphotropic virus responsible for polyclonal B-lymphocyte expansion that leads to the development of extrahepatic manifestations, such as type II cryoglobulinemia and some types of B-cell non-Hodgkin lymphomas, such as lymphoplasmacytic lymphoma/immunocytoma and marginal-zone lymphomas. In addition, chronic HCV infection is considered a trigger for immune-mediated disorders through a crossover immune response to self-antigens due to sequence similarities between viral proteins and self-proteins (molecular mimicry theory) or through the activation of autoreactive T-cells due to viral-induced local inflammation (bystander activation theory). In fact, chronic HCV infection has been associated with autoimmune diseases such as psoriasis, lichen planus, Sjogren syndrome and autoimmune thyroiditis, with the presence of organ-specific circulating anti-thyroperoxidase and anti-thyroglobulin autoantibodies and with high titers of non-organ-specific antinuclear, anti-smooth muscle and anti-liver/kidney microsome autoantibodies.

Patients with HCV infection show an increased overall mortality compared to the normal population, probably related to a dysmetabolic syndrome and cytokine remodeling towards chronic systemic inflammation that triggers endothelial dysfunction in response to the HCV envelope protein.

Luckily, recent advances in anti-HCV therapy have led to more efficient well tolerated interferon-free DAA regimens, so most patients can achieve HCV eradication. Ninety-five per cent of CHC patients without cirrhosis treated with DAAs recover completely, but substantial clinical and sometimes even histological improvement is also observed in cirrhotic patients. The beneficial action of the eradication of HCV infection with DAAs is also exerted on the extra-hepatic manifestations of this infection, but some results are contradictory or difficult to explain.

In fact, the available data do not allow a conclusion on whether the eradication of HCV infection induces a persistent reduction in fasting glucose and HbA1c; nevertheless, most studies strongly indicate a good T2DM compensation in patients treated with DAAs. Further long-term prospective studies on the evolution of glucose metabolism in HCV patients who achieved SVR with DAA treatment, diabetic and non-diabetic, are needed to resolve the remaining disputes.

CHC patients frequently show low serum levels of Total and LDL cholesterol, which increase significantly after HCV eradication, in some cases beyond the pre-treatment levels, most likely because the interaction between interaction HCV / lipid metabolism ceases. Despite this negative effect, HCV eradication exerts an overall favorable action on the cardiovascular system, possibly eliminating numerous other harmful effects exerted by HCV on this system.

Mechanisms responsible for direct vascular and cardiac damage in HCV patients have been identified in the procoagulant imbalance and in the IR/T2DM ratio. Furthermore, HCV-core protein can induce an immune-mediated oxidative damage in myocardial tissue and is considered a direct cardiotropic virus, responsible for dilated, hypertrophic right ventricular arrhythmogenicity, cardiac fibrosis and myocarditis. An association has been observed between carotid atherosclerosis, carotid intima-media thickness, β stiffness and HCV core protein. Other studies have reported an increased risk of acute coronary syndrome (ACS) and acute myocardial infarction (AMI), with an association between the number of affected vessels and HCV viral load. The abolition of many negative effects due to DAA induced HCV eradication explains how the increase in IR, Total and LDL cholesterol induced by the same drugs are not very influential. In this regard, it should be also considered that the increase in IR is transitory and therefore has only a temporary negative influence.

Infecting kidney endothelium, tubular epithelial cells, renal infiltrating leukocytes and mesangial cells, HCV is responsible of several kidney lesions, like mixed cryoglobulinemic nephropathy, membranous-proliferative glomerulonephritis, and membranous nephropathy. This infection speeds CKD to an end-stage and has been identified as an independent predictor of death for dialysis patients. The DAAs-induced HCV eradication exerts a beneficial effect in CHC patients with CKD, even in those HIV coinfected, but some conflicting data persist on the effect of some DAA regimens on eGFR. Indeed, the favorable effect of DAA on eGFR is more evident in patients with mild or moderate CKD (stages CKD-3a/CKD-3b) than in those with a more severe illness (stages CKD-4/5).

HCV infection is associated with both mixed cryoglobulinemia and non-Hodgkin's lymphoma, particularly B-cell NHL. MCS is currently considered as a B-cell benign lymphoproliferative disorder frequently induced by HCV infection, but it is also associated with autoimmune or lymphoproliferative disorders. HCV-induced MCS frequently shows a silent, indolent course, but in some cases, it may present a rapidly unfavorable, sometimes life-threatening outcome. Nearly 20% of HCV-related MCS patients show nephropathy at the time of first diagnosis, an index of unfavorable prognosis. DAA treatment finds full application in CHC patients with MCS, since it has a good safety profile, induces HCV eradication in nearly 95% of treated patients and

is associated with remissions of cryoglobulinemic vasculitis and with a reduction extrahepatic mortality. In addition, MCS infrequently occurs in CHC patients after HCV eradication.

The role of HCV virus in the pathogenesis of lymphoproliferative diseases have been shown by several epidemiological studies and is now worldwide accepted. Available studies increasingly recognize the beneficial role of DAAs-induced HCV eradication in treating of HCV-related lymphoproliferative disorders. Antiviral therapy appears majorly important in patients with low-grade B-NHL, but some recent information support using DAAs to obtain HCV eradication also in patients affected by the more aggressive form NHL and even in HVC-positive DLBCL, in this case in combination with chemotherapy.

In conclusion, DAA-induced HCV eradication influences favorably all the extrahepatic manifestations of this infection, with the exception of lipid homeostasis, where the increase in TC and LDL cholesterol could favor, at least theoretically, the occurrence of cardiovascular events. This eventuality, however, is poorly perceived in most cases, possibly because overwhelmed by the effect of HCV eradication in abolishing numerous other harmful effects of HCV infection on cardiovascular system.

Conflict-of-Interest Statement All the authors of the manuscript declare they have no conflict of interest in connection with this paper.

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