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REVIEW

Cardiometabolic effects of direct-acting antivirals in patients with hepatitis C

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Abstract Hepatitis C virus (HCV) has long been associated with several extrahepatic manifestations, including increased cardiovascular risk. The emergence of direct-acting antivirals (DAAs) has allowed us to evaluate the potential reversal of these manifestations after successful treatment. Therefore, many studies have provided significant takeaways regarding the positive effect of DAAs therapy on insulin resistance, type 2 diabetes mellitus, cardiovascular disease and atherosclerosis. In contrast, studies have shown detrimental effects on lipid metabolism and indeterminate results regarding renal function and uric acid metabolism. Nevertheless, as more and more patients achieve sustained virological response, the effects of HCV eradication on cardiometabolic processes will be extensively studied, allowing more reliable conclusions on the extent of extrahepatic outcomes.

PALABRAS CLAVE
Antivirales de acción directa;
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Función renal

Efectos cardiometabólicos de los antivirales de acción directa en pacientes con hepatitis C

Resumen El virus de la hepatitis C (VHC) se ha asociado durante mucho tiempo a varias manifestaciones extrahepáticas, entre ellas el aumento del riesgo cardiovascular. La aparición de los antivirales de acción directa (AAD) ha permitido evaluar la posible reversión de estas manifestaciones tras un tratamiento exitoso. Así, muchos estudios han aportado datos significativos sobre el efecto positivo del tratamiento con AAD en la resistencia a la insulina, la diabetes mellitus de tipo 2, la enfermedad cardiovascular y la aterosclerosis. Por el contrario, los estudios

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han mostrado efectos perjudiciales sobre el metabolismo de los lípidos y resultados indeterminados respecto a la función renal y el metabolismo del ácido úrico. No obstante, a medida que un mayor número de pacientes logre una respuesta virológica sostenida, se estudiarán ampliamente los efectos de la erradicación del VHC sobre los procesos cardiometabólicos, lo que permitirá obtener conclusiones más fiables sobre el alcance de los resultados extrahepáticos.

Introduction

Chronic hepatitis C virus (HCV) infection affects 1–2% of the world population. HCV is associated with extrahepatic manifestations such as lymphoproliferative processes, autoimmune, cardiovascular, renal and nervous system diseases. Insulin resistance (IR) is reported in up to 70% of cases, and HCV infection has been associated with the development of type 2 diabetes mellitus (T2DM).[1] HCV enhances its replication by modulating host cell lipid metabolism. Many lipids are crucial for the virus life cycle, while inhibitors of cholesterol/fatty acids biosynthetic pathways suppress viral replication.[2] Moreover, recent data have identified HCV infection as a risk factor for cardiovascular disease (CVD), leading to increased mortality and morbidity. Additionally, atherosclerosis is identified as a result of HCV infection due to chronic HCV infection causing liver and systemic inflammation via increased levels of pro-atherogenic chemokine and cytokines.[3] Another complication of HCV infection is the increased risk of chronic kidney disease (CKD). HCV and CKD are related for 2 main reasons: first, because patients with CKD can be exposed to the virus through dialysis, and second because HCV infection can induce renal disease.[4] Finally, elevated uric acid levels represent an independent risk factor for more advanced steatosis in this population.[5,6]

Direct-acting antivirals (DAAs) have revolutionized the treatment of chronic HCV infection. Accumulating data suggest that these agents exert a wide range of effects on cardiovascular risk factors, which are partly due to HCV eradication. The present review aims to summarize the current evidence on the effects of DAAs on cardiometabolic risk factors and CVD.

Literature search

We conducted a thorough search on the Pubmed, Google Scholar and Cochrane Library databases through February 2021. Search terms included ''DAAs'', ''Direct Acting-antivirals'', ''Hepatitis C eradication'', ''sustained virological response'' ''SVR'' and according to the relevant topic: ''Diabetes mellitus'', ''DM'', ''T2DM'', ''glucose'', ''insulin resistance'', ''insulin sensitivity'', ''CKD'', ''chronic kidney disease'', ''renal function'', ''CVD'', ''cardiovascular disease''. ''cardiac'', ''heart disease'', ''coronary disease'', ''atherosclerosis'', ''hypertension''. ''lipids'', ''dyslipidemia'', ''cholesterol'', ''triglycerides'', ''uric acid'', ''metabolic'', ''extra-hepatic''. Furthermore, we examined the references of selected studies and relevant reviews for unidentified studies.

Effect of direct-acting antivirals on the lipid profile

Several studies showed that HCV alters the host lipid metabolism. Processes, such as viral replication, virion circulation and hepatocyte entry, rely on host lipids' interactions.[2,7] The results of these interactions include hepatic steatosis, hypobetalipoproteinemia and hypocholesterolemia.[8]

Newer DAAs induce sustained virologic response (SVR) in almost all treated patients. HCV clearance after treatment with these agents restores gradually the metabolic disturbances observed during chronic HCV infection. Accordingly, numerous studies reported an increase in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) after treatment with DAAs (Table 1). This increase is rapid in almost all studies and occurs by week 4 of treatment, with slower increases until the end of treatment and at 1 year after treatment. The rapid clearance of HCV by the new DAAs appears to underpin these changes.

Regarding the effects of DAAs on other lipids, serum high-density lipoprotein cholesterol (HDL-C) levels increased in some studies but did not change in others. In contrast, triglyceride (TG) levels did not change in most of the studies. Apolipoprotein (apo) levels were also affected by HCV clearance.[9–13] An increase was found in the levels of Lp(a),[11] apoB,[10,13] apoB/apoA1 ratio[11,12] and apo C2,[9,13] whereas a decrease was reported in the levels of apoA2 and apoE.[9,10,13]

HCV genotype, HCV/HIV co-infection and the presence of advanced fibrosis or cirrhosis do not appear to modify the effect of HCV eradication on lipid metabolism. Morales et al reported that the increase in TC and LDL-C levels was irrespective of antiviral therapy or genotype, suggesting that these changes are most likely related to viral clearance than to a direct pharmacological effect.[14] Townsend et al. showed that HIV co-infection does not substantially modulate the HCV-induced perturbation in serum cholesterol levels.[15] In a study by Doyle et al., the presence of cirrhosis did not affect lipid levels during or after treatment.[13] Finally, many of the cohorts included mixed populations with different HCV genotypes, stages of liver fibrosis and HIV co-infection status but still yielded similar results.

Gene polymorphisms and their impact on lipid metabolism after achieving SVR with DAAs were studied in two clinical trials. Morihara et al. focused on IL28B

Table 1 Characteristics and results of studies investigating the effect of therapy with DAAs on serum lipids.

Study	Patients	Therapy	Genotype	Δ_{CHOL} (%)	Δ_{LDL}(%)	Δ_{HDL} (%)	Δ_{TRIG} (%)
Chida[10]	70	DCV + ASV	1b	+6.9%	+ 9.6%	+ 12%	
Gitto[11]	100	DAAs	All	+ 10.4%	+ 27.5%	NS	NS
Meissner[12]	60	SOF + RBV	1		+ 27.8%		− 9.5%
Doyle[13]	24	PrOD ± RBV	1a + b	+ 6.8%	+ 11.5%	+ 8.3%	+ 38.5%
Morales[14]	60	SOF regimen	1, 2, 3	+ 16.4%	+ 28.9%	NS	NS
Townsend[15]	90	SOF/LDV	1	+ 15.7%	+ 28.1%	+ 10.6%	NS
Morihara[16]	121	DCV/ASV for 24 weeks - (OBV/PTV/r for 12 weeks − SOF/LDV for 12 weeks		+ 11.9%	+ 24.2%	+ 7.8%	NS
Emmanuel[17]	301	DAAs	1		+ 24%	NS	− 13.4%

SOF: Sofosbuvir, RBV: Ribavirin, DCV: Daclatasvir, ASV: Asunaprevir, LDV: Ledipasvir, DAAs: Direct-acting antivirals, PEG-IFN: Pegylated interferon, PrOD: Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir, OBV/PTV/r: Ombitasvir/Paritaprevir/Ritonavir, Δ: Change (%), CHOL: Total cholesterol, TRIG: Triglycerides, NS: non-significant.

gene polymorphisms and their effect on lipid levels.[16] Patients with the IL28B TG/GG genotype experienced larger increases in LDL-C levels after treatment than patients with the TT genotype. In a study by Emmanuel et al, carriers of the IFNL4 ΔG/TT or $\Delta G/\Delta G$ alleles showed an increase in LDL-C levels after treatment with DAAs whereas carriers of the IFNL4 TT/TT allele showed no change in LDL-C levels.[17]

In liver transplant recipients, treatment of recurrent HCV infection with DAAs reversed the virus's hypolipidemic effect in a study by Beig et al.[18] Serum TC and LDL-C levels increased at 41 weeks post-treatment and this increase was independent of dose and trough levels of immunosuppressive therapy and body weight changes. Studies investigating the effects of DAA treatment on the patient's lipid profile are summarized on Table 1.

Effects of DAAs on IR and T2DM

It has been shown that HCV infection induces IR in the liver and peripheral tissues.[1] Indeed, IR is present in 30–70% of patients with HCV infection.[1] Accordingly, patients with HCV infection are 67% more likely to develop T2DM than HCV-negative subjects.[19]

Several studies showed that direct-acting antiviral (DAA) treatment improves insulin sensitivity. In a prospective case-control study ($n = 133$ patients without T2DM), 76.5% of patients who achieved sustained virological response following treatment with DAA showed improvement in IR, of which 41.2% had normal insulin sensitivity after treatment.[20] In a more extensive report in 511 patients with HCV infection (24.7% with T2DM), SVR following DAA treatment also resulted in improved insulin sensitivity.[21]

A number of studies also reported a reduction in fasting plasma glucose (FPG) and HbA_{1c} levels after treatment with DAA in patients with HCV infection and T2DM.[22,23] It has also been observed that HbA_{1c} levels decrease more in patients who achieve SVR following DAA treatment than those who do not or in those who relapse.[24] Notably, this improvement in glycemic control appears to be sustained during long-term follow-up. In a study in 122 patients with T2DM, 33% of patients showed improved glycemic control after DAA treatment (defined as a decrease in $HbA_{1c} > 0.5\%$ with no change in antidiabetic treatment or a decrease in the number of antidiabetic medication with no change in HbA_{1c}), which was sustained in 71% of them during a follow-up period of 1.5 years.[25] These benefits also appear to be present in special populations. In a retrospective, single-center study in 91 liver transplant recipients with recurrent HCV infection, eradication of HCV infection with DAA treatment was associated with a reduction in HbA_{1c} levels and the number of antidiabetic medications.[18]

Treatment with DAA also appears to reduce the risk of new-onset T2DM. In an early study in 82 patients (38% with prediabetes and 17% with T2DM), DAA treatment resulted in SVR in all patients along with a decrease in glucose and insulin plasma concentration.[26] Moreover, the prevalence of prediabetes declined to 21% after treatment, particularly in patients who were more insulin resistant as evaluated with the homeostasis model assessment. More importantly, in a recent study in 21,279 patients with HCV infection but without T2DM, treatment with DAA reduced the incidence of T2DM by 53% compared with no treatment or treatment with interferon/ribavirin.[27] Of note, patients who advanced fibrosis showed more significant reductions in the incidence of T2DM after treatment with DAA.

Effect of direct-acting antivirals on uric acid levels

Few data are available regarding uric acid levels in patients with chronic hepatitis C. Elevated uric acid levels appear to represent an independent risk factor for more advanced steatosis in this population.[5] In contrast, serum uric acid levels are inversely associated with the severity of fibrosis.[28]

Limited data also exist on the effects of DAAs on serum uric acid levels. Sato et al. reported a transient increase in serum uric acid levels during combination therapy with sofosbuvir and ribavirin.[6] Uric acid levels reached a maximum on week 1 of treatment and then gradually dropped to pre-treatment levels at the end of treatment. A num-

ber of possible pathogenetic mechanisms were proposed, such as potential renal toxicity of SOF or RBV, a rapid disruption of HCV RNA that might affect purine metabolism, dose-dependent hemolytic anemia caused by RBV, and possible interactions between SOF and xanthine oxidoreductase (XOR) or breast cancer resistance protein (BCRP). In contrast, in a prospective cohort study by Jang et al. in 213 patients with chronic HCV infection, a decrease in serum uric acid levels and the prevalence of hyperuricemia was observed after treatment with DAAs, but only in patients with a fibrosis-4 index (FIB-4) < 6.5.[29]

Effects of treatment with DAAs on renal function

HCV has a detrimental effect on kidney function[4] and CKD is more prevalent in patients with chronic HCV infection than in the general population.[30] Accordingly, and because of the high HCV prevalence in patients undergoing dialysis,[4] many studies investigated the effects of antiviral therapy on renal function in patients with chronic HCV infection. Studies that evaluated IFN-based treatment demonstrated improvements in glomerular filtration rate (GFR) in patients achieving SVR, even in special populations such as patients undergoing hemodialysis or in those who had received liver transplantation.[31–33] More recently, 2 studies evaluated both IFN-based and IFN-free combinations. Park et al evaluated the effect of antiviral treatment on CKD development in 55,818 patients with HCV, among which 11,828 patients received therapy, with 4628 receiving all-oral DAA treatment and the rest receiving IFN-based treatment.[30] While treatment was associated with a lower risk for CKD (hazard ratio (HR) 0.70), this benefit was observed only in patients who received IFN-based therapy. Perez de Jose et al evaluated renal outcomes in 139 patients with HCV-associated mixed cryoglobulinemia, of whom 100 received DAA therapy, 24 IFN-based therapy and 15 were untreated, during a follow-up period of 138 months.[34] Patients receiving DAAs had significantly less risk (HR 0.10, $p < 0.001$) of receiving renal replacement therapy (RRT) or experiencing a two-fold increase in baseline serum creatinine levels. Additionally, a reduction in albuminuria was observed in patients treated with DAAs.

Several studies evaluated the effects of DAAs on GFR. Mehta et al analyzed 3319 patients treated with the combination of ombitasvir-paritaprevir-ritonavir plus dasabuvir (3D) from 3 different trials and reported that GFR decreased in patients with normal renal function ($p < 0.001$) and did not change in patients with CKD.[35] In another study in 13,663 patients receiving SOF + ledipasvir (LED) and 3961 patients receiving 3D, 30–38% of patients showed a decline of >10 ml/min/1.73 m^2 in GFR at 12 weeks after treatment; in contrast, among patients with stage 4 and 5 CKD, only 0–6% showed a decline in GFR.[36] In a study by Chiu et al in a cohort of 1536 HCV patients treated with 4 different DAAs regimens, GFR decreased at 48 weeks post-treatment compared with baseline ($p < 0.05$).[37] Finally, a study by Sise et al. evaluated patients 3 years after DAA treatment a reported a reduction in the rate of GFR decline in patients with GFR < 60 ml/min/1.73 m^2 ($p < 0.0001$) and a faster decline in patients with GFR > 60 ml/min/1.73 m^2 ($p = 0.01$).[38]

Many studies evaluated SOF-based regimens' effect on renal function because SOF has a primarily renal elimination and is not recommended in patients with GFR < 30 ml/min/1.73 m^2.[39] Aby et al reported that among patients treated with SOF-based regimens ($n = 523$), those who achieved SVR had a similar change in GFR with untreated patients. In contrast, patients not achieving SVR had a significant deterioration in GFR (mean 11 ml/min/1.73 m^2, $p < 0.005$).[40] Similarly, in 5 studies evaluating SOF-based treatments in patients with concomitant HIV infection, GFR did not change after treatment.[41,42] Furthermore, in a study by Liu et al in 308 patients treated with SOF-based and 173 treated with SOF-free regimens,[43] the latter showed an improvement in GFR both during and after treatment, whereas those treated with SOF-based regimens experienced a reduction in GFR during therapy and a smaller improvement post-therapy. In contrast, Coppola et al. reported that patients treated with SOF-based regimens had an increase in GFR post-treatment, whereas patients on SOF-free regimens had no change in GFR.[44] Notably, patients with CKD or cirrhosis at baseline experienced an increase in GFR, whereas those without CKD or cirrhosis showed no change in GFR. Conversely, in a study by Chen et al, patients with cirrhosis undergoing treatment with SOF-based regimens showed decreased GFR, whereas those without cirrhosis did not.[45]

A number of studies evaluated the effects of DAAs on renal function in patients with HCV infection who had undergone liver transplantation. Notably, Beig et al reported an increase in GFR in 97 patients receiving DAA therapy ($p < 0.001$).[18] Studies evaluating the effects of DAA therapy on renal function are summarized in Table 2.

Effects of treatment with DAAs on cardiac function

Conflicting data have been reported regarding the effects of DAAs on cardiac function. Mazzitelli et al. evaluated global longitudinal strain (GLS) and ejection fraction (EF) in 82 patients before and 24 weeks after treatment with SOF-based DAAs. While EF did not change, GLS worsened at the end of the follow-up period (mean GLS increase 0.07/month, $p < 0.05$).[46] In contrast, another study reported decreased left and right atrial and right ventricular volume at 6 months after the end of therapy with DAAs in 56 non-obese, non-diabetic patients with low fibrosis score.[47]

Impact of DAA treatment on subclinical atherosclerosis

Chronic HCV infection is associated with an increased prevalence of subclinical atherosclerosis.[3] Recently, a number of studies evaluated the effects of DAA treatment on subclinical atherosclerosis. In a multicenter study in 182 consecutive HCV patients with advanced fibrosis (F3) or compensated cirrhosis (66% of patients), carotid intima-media thickness and the proportion of patients with carotid thickening decreased 9–12 months after the end of DAA therapy.[48] In another recent study in 114 patients, treatment with DAAs improved endothelial function and reduced the ankle-brachial index,

Table 2 Studies investigating the effect of treatment with DAAs on renal outcomes.

Study/year type	Mean follow-up	Population/regimens	SVR	Significant outcomes
Park[30]/2018 Retrospective	First CKD diagnosis	DAAs: 4628 IFN-based: 7200 Untreated: 43,990	?	Treatment associated with reduced incidence of CKD, only in IFN-based group
Perez de Jose[34]/2020 Retrospective	138 months	DAAs: 100 IFN-based: 24 Untreated: 15	DAAs: 98%	DAAs treatment associated with reduced risk of renal events (dialysis, 2× creatinine elevation)
Mehta[35]/2020 Phase 3 trials	52 weeks post-treatment	3319 patients under PrOD ± RBV	95–97.6%	Significant GFR decrease in CKD stage 1 patients
Butt[36]/2018 Retrospective	12 weeks post-treatment	PrOD ± RBV: 3961 SOF-LDV ± RBV: 13663	98%	GFR: Decline > 10 ml/min/1.73 m^2 in 30–38% of patients
Chiu[37]/2020 Retrospective	Three years pre- and post-treatment	DAAs: 1536 Cirrhosis: 59%	?	Treatment associated with significant GFR decrease
Sise[38]/2020 Retrospective	6 months post treatment	DAAs: 1178	93%	Increase decline of GFR in patients with GFR > 60 compared to patients with <60
Aby[40]/2017 Retrospective	12 weeks post-treatment	SOF-based: 523 Untreated: 439 Cirrhosis: 49%	93%	GFR: No difference between SVR and untreated patients, significant decline in non-SVRpatients
Soeiro[41]/2018 Prospective	12 weeks post-treatment	HIV/HCV (n = 273) Sof-based	99%	GFR: decrease during treatment, recovery to baseline levels at week 12 post-treatment
Taramasso[42]/2017 Prospective	12 weeks post-treatment	HIV/HCV (n = 79) Sof-based	88%	Insignificant change in GFR during treatment and follow-up
Liu[43]/2020 Retrospective	24 weeks post-treatment	SOF-based: 308 SOF-free: 173	98%	SOF-free: on- and off-therapy GFR improvement SOF-based: on therapy worsening, off-therapy improvement
Coppola[44]/2019 Prospective	12 weeks post-treatment	SOF-based: 280 SOF-free: 123 Cirrhosis: 36%	98%	GFR improvement in patients with cirrhosis, CKD and treated with SOF-based regimens
Chen[45]/2017 Retrospective	24 weeks post-treatment	SOF-based: 43 Cirrhosis: 42%	93%	Cirrhosis: significant GFR decrease
Beig[18]/2018 Retrospective	24 weeks post-treatment	LT patients (n = 91) DAAs	96%	Treatment associated with significant GFR increase

SVR: Sustained viral response, CKD: Chronic kidney disease, DAA: Direct acting antiviral, IFN: Interferon, PrOD: Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir, RBV: Ribavirin, SOF: Sofosbuvir, GFR: Glomerular filtration rate, LDV: Ledipasvir, HIV: Human Immunodeficiency virus, HCV: Hepatitis C virus, LT: Liver transplantation.

a marker of peripheral arterial disease, in patients with endothelial dysfunction and subclinical atherosclerosis at baseline, respectively.[49] In contrast to these beneficial effects of DAAs on subclinical atherosclerosis, a prospective study in 102 patients treated with DAAs reported an increase in arterial stiffness, evaluated with the augmentation index and central blood pressure, in patients with advanced fibrosis after SVR but not in those with no or mild fibrosis.[50]

Effects of DAAs on cardiovascular events

Chronic hepatitis C appears to be associated with increased cardiovascular morbidity.[51,52] A small number of early studies suggested that IFN-based therapies might improve cardiovascular outcomes.[31,53] More recently, a number of studies compared the effects of IFN-based and IFN-free regimens on cardiovascular events. Nahon et al. evaluated the risk of major adverse cardiovascular events (MACE), including stroke, ischemic heart disease, cardiovascular death, cardiac arrest, and heart failure in 1323 patients with cirrhosis after HCV treatment.[54] One-fourth of the patients received IFN-free combinations. SVR was observed in 50.5% of patients and was associated with a lower risk for cardiovascular events (HR 0.49, $p < 0.01$) and MACE (HR 0.53, $p < 0.05$) after a mean follow-up of 58 months. In a more recent analysis from the same group (n = 878), SVR was again independently associated with a lower risk for MACE (HR 0.35, $p < 0.05$).[55] Another study investigating the effect of HCV treatment on the incidence of cardiovascular events was undertaken using a large database in the US and by matching patients treated with both IFN-free (n = 12,467) and IFN-based (4436) regimens with untreated controls.[56]

Table 3 Studies investigating the effect of treatment with DAAs on cardiac outcomes.

Study/Year Type	Mean follow-up	Population/ Regimens	SVR	Significant Outcomes	
Nahon[54]/2017 Retrospective	58.2 months	Cirrhosis IFN-free: 328 IFN-based: 995	50.5%	SVR associated with reduced risk of CVD and MACE	
Singer[58]/2017 Retrospective	350 days	Untreated: 96252 DAAs: 13125	?	Treatment associated with reduced risk of cardiac and cerebrovascular events	
Carrero[59]/2020 Prospective	96 weeks post-treatment	HIV/HCV: 237 IFN-free: 89% IFN-based: 11%	62%	Decrease of CVD risk score only in patients with SVR	
Butt[56]/2019 Retrospective	First CVD event	DAAs: 12667 IFN-based: 4436 Untreated: 17103	76%	Treatment vs no treatment DAAs vs IFN	Lower risk of CVD events
Adinolfi[57]/2020 Prospective	28 months	DAAs: 1668 Untreated: 486	98.2%	Treatment/SVR: Lower risk for CVD events	

SVR: Sustained viral response, CVD: Cardiovascular disease, MACE: Major adverse cardiovascular events, DAA: Direct acting antiviral, IFN: Interferon, SOF: Sofosbuvir, HIV: Human Immunodeficiency virus, HCV: Hepatitis C virus.

Both treatment with DAAs and with IFN-based regimens were associated with reduced incidence of cardiovascular events (HR 0.57 and HR 0.78 respectively, $p < 0.0001$), irrespective of SVR. Interestingly, in a sub-analysis, patients treated with DAAs had a lower incidence of cardiovascular events than patients treated with IFN-based regimens (HR 0.8, $p < 0.05$). Adinolfi et al. prospectively evaluated 1668 patients treated with DAAs and 486 untreated patients as controls[57] and reported after a median follow-up of 28 months that SVR was associated with reduced risk of cardiovascular events (relative risk (RR) 0.38, $p < 0.001$). Another study compared 13,125 patients treated with DAAs and 96,252 untreated patients followed-up for 350 days and reported a lower incidence rate of cardiac (RR 0.71) and cerebrovascular (RR 0.74) events in the former.[58] Finally, one study addressed the effect of HCV treatment on estimated cardiovascular risk as assessed by the Framingham study risk equation in 237 patients with HIV/HCV co-infection[59] receiving mainly IFN-based treatment (90%). Patients who achieved SVR showed a decrease in estimated cardiovascular risk ($p = 0.05$), while patients who did not achieve SVR showed no change in risk ($p = 0.433$). Studies evaluating the effects of DAA therapy on cardiovascular eventsare summarized in Table 3.

Conclusions

Nowadays, DAA's are the cornerstone treatment of HCV, effectively minimizing liver-related outcomes in patients achieving SVR and spearheading the World Health organizations' plan for the global eradication of HCV by 2030.[60] Additionally, HCV eradication's effects seem to expand to extrahepatic processes and diseases. Increased insulin resistance is a well-documented effect of HCV,[20,21] leading to significant benefits in insulin sensitivity and T2DM incidence or control in patients treated with DAAs. Additionally, data suggest that treatment with DAAs reduces the risk of CVD and stroke incidence in patients with HCV infection compared with untreated patients. Combined effects on atherosclerosis, insulin resistance and oxidative stress are proposed as the mechanisms behind this outcome.[3] Existing studies appear conflicting regarding the long-term effect of DAAs on renal function. However, most studies point towards a succinct renal function trajectory during and after DAAs therapy, with GFR trending downwards during therapy and upwards after the end of treatment. In conjunction with the limited length of follow-up of most studies (due to the relatively recent emergence of DAAs), this fact may indicate long-term renal function improvement as a consequence of DAAs therapy. Furthermore, given that chronic HCV infection is associated with increased cardiovascular risk,[52] the increase in LDL-C levels after achieving SVR with the new DAAs and its associated cardiovascular implications are a reason of concern. Accordingly, monitoring of lipid levels and, when appropriate, administration of lipid-lowering agents are recommended. Finally, although an elevated uric acid may represent a risk factor for advanced steatosis in this population, more studies are needed to ensure this hypothesis. To sum up, the massive eradication campaigns inspired by the emergence of DAAs have started to uncover the magnitude of extrahepatic effects of HCV and its subsequent eradication. DAA treatment's effects seem to be mostly beneficial, with a few exceptions, such as the effects on lipid metabolism. Nevertheless, as we move further away from the beginning of the DAA era, these effects will be more pronounced and easier to quantify. Therefore, in the next few years, more studies are expected, which would provide definitive answers regarding the effect of DAAs treatment on significant cardiometabolic processes.

Conflict of interest

None.

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