

Treatment of hepatitis C virus infection and associated glomerular disease

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ABSTRACT

Hepatitis C virus infection is a systemic disorder and can have various extrahepatic manifestations like hepatitis virus C associated glomerulonephritis. KDIGO recommends that all patients with hepatitis C virus infection be tested at least annually for proteinuria, hematuria and eGFR in order to detect a possible HCV-associated kidney disease. Immunosuppressive therapy must be initiated in patients who have severe complications due to hepatitis virus C infection, but the clinicians must consider two aspects: hepatotoxicity and viral reactivation due to immunosuppression. As for antivirals, DAAs are now first-line treatment for management of HCV infection, even in CKD patients with advanced renal disease. In this review, we aimed to take a look on possible therapies for HCV-induced glomerulonephritis, the interactions between them and the impact of different therapies on renal and hepatic diseases.

Keywords: hepatitis C virus, immunosuppression, DAAs, CKD, glomerulonephritis

INTRODUCTION

Hepatitis C virus (HCV) infection is a systemic disorder which can have numerous extrahepatic manifestations, including various types of renal diseases.

Renal manifestations of hepatitis C virus infection include nephrotic syndrome, nephritic syndrome, non-nephrotic proteinuria and microscopic hematuria [1]. The incidence of hepatitis C virus-associated nephropathy is still unknown, because large population studies are lacking, but a higher prevalence of CKD (chronic kidney disease) and a shorter time interval from the first signs of renal disease to ESRD (end stage renal disease) are related to hepatitis C virus infection [2-4].

KDIGO recommends that all patients with hepatitis C virus infection be tested at least annually for proteinuria, hematuria and eGFR (glomerular filtration rate) in order to detect a possible HCV-associated kidney disease.

TABLE 1. KDIGO recommendations [5]

A kidney biopsy is recommended if HCV-infected patients have clinical evidence of a glomerular disease (not graded)
Patients with HCV-associated glomerular disease should be treated for HCV. (1A)
Patients who show stable kidney function and/or non-nephrotic proteinuria should be treated initially with DAAs (direct acting antivirals) (1C)
Patients with cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure should be treated, in addition to DAA treatment, with immunosuppressive agents with or without plasma exchange (1C)
Patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease should receive immunosuppressive therapy. (1B)
Rituximab is recommended as first-line treatment. (1C).

ANTIVIRAL THERAPY AND RENAL DISEASE

Antiviral therapy clears HCV and improves renal disease. The impact of antiviral treatment on

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HCV-associated glomerular disease was studied in case reports and small observational studies. Initial studies included patients treated with IFN in monotherapy or mixed therapy – IFN and ribavirin. Although nowadays interferon is replaced by DAAs, IFN (interferon) gave important information about the role of hepatitis C virus in the pathogenesis of glomerulopathies.

The treatment of patients with HCV-associated glomerulonephritis must be guided by the severity of proteinuria and the stage of renal disease. Patients with CKD stage 4 and 5 have shown a low tolerance for interferon therapy, and time exposure was longer because of decreased renal clearance [6] and when RBV (ribavirin) was associated to interferon in CKD stage 3b and 5 patients, hemolytic anemia was frequent and could sometimes be severe [7]. Cases of membranous nephropathy [8], minimal change disease, GSFS (focal segmental glomerulosclerosis) were described as secondary to IFN treatment [9], as IFN can unmask/trigger an autoimmune process [10,11] and could even trigger de novo vasculitis which would need corticotherapy [12-14].

DAAs should be first-line treatment in patients with non-nephrotic proteinuria and a relatively stable renal function, as these patients could have proteinuria remission and an improvement in GFR if they obtain SVR (sustained virologic response). Different studies found an improvement in histologic renal lesions in patients who were rebiopsied at the end of antiviral treatment after the clearance of HCV-RNA [15,16].

Even though there is no data which could demonstrate that 12-weeks SVR reduces CKD mortality, a meta-analysis showed that 24-weeks SVR is a mortality predictor in general population [17-19].

Nevertheless, the clinical benefit in patients who obtain SVR can be temporary and/or a dissociation between viral response and renal response could happen no matter of the antiviral of choice (IFN or DAAs), with an unclear long-term impact over the renal disease. Vasculitic manifestations could appear despite SVR, but usually they also

improve after SVR was obtained during DAAs treatment [20].

KDIGO supports the idea that DAAs are efficient and well tolerated and usually they do not need dose adjustments in CKD patients, but when immunosuppressive therapy is co-administered, the clinicians must consider possible interactions. Cyclosporine and mTOR inhibitors are metabolized in the liver by the cytochrome P450. Thus, substrate competition can occur for DAAs and these immunosuppressants [21,22].

TABLE 3. Pharmacokinetics of DAAs in CKD patients [25]

DAA	Elimination
Sofosbuvir	Renal 80%
Dasabuvir	GI 90%; Renal < 2%
Daclatsvir	GI 88%; Renal 6%
Ledipasvir	GI 86%; Renal 1%
Ombitasvir	GI 90%; Renal < 2%
Elpasvir	Renal < 1%
Velpatasvir	GI 77%
Simeprevir	GI 91%; Renal < 0.4%
Paritaprevir/Ritonavir	GI 90%; Renal < 2%
Grazoprevir	Renal < 1%

DAA: direct-acting antiviral; GFR: glomerular filtration rate; GI: gastrointestinal; AUC: area under the curve

EASL guide recommends dosing DAAs as in normal renal function in CKD patients, with the condition of a strict monitoring. Sofosbuvir was initially approved just for patients with a GFR > 30 ml/min, but in November 2019, the FDA approved Sofosbuvir for patients with severe renal disease, including those on dialysis [24].

RUBY-I study showed that the regimen ombitasvir/paritaprevir/ritonavir is well tolerated and has high SVR rates (including patients with compensated cirrhosis and/or prior treatment experience) in patients with hepatitis C virus genotype 1 or 4 infection and stage 4 or 5/5D CKD. Also, DAAs plasma concentrations were not affected by renal disease or dialysis and they do not need dose adjustments. Even more, HCV-infected dialysis patients have lower plasma HCV RNA levels than

TABLE 2. Immunosuppressive therapy and DAAs interactions [23]

Medication	SOF/LDV	SOF	SMV	OMV/PTV/r/DSV	EBR/GZR
TAC	↔ TAC level	↔ TAC levels	↓ TAC levels	↑ TAC levels (ritonavir)	↑ TAC levels
CyA	↔ CyA levels	↔ CyA levels	↑ CyA and SMV levels	↑ CyA levels (ritonavir)	GZR levels; contraindicated association
SRL	↔ SRL levels	↔ SRL levels	↑ ↓ / SRL levels	↑ SRL levels (ritonavir)	↑ SRL levels

CyA: cyclosporine; EBR/GZR: elbasvir/grazoprevir; LDV: ledipasvir; OMV/PTV/r/DSV: ombitasvir / paritaprevir / ritonavir / dasabuvir; SMV: simeprevir; SOF: sofosbuvir; SRL: sirolimus; TAC: tacrolimus

↔ No changes in plasma levels; ↓ Decrease in plasma levels; ↑ Increase in plasma levels

HCV-infected patients with normal renal function and may be easier to treat. Despite the use of a low dose of RBV, this therapy was interrupted in a high percentage of patients due to anemia [26].

C-SURFER evaluated the efficacy and safety of Elbasvir/Grazoprevir combination in patients with CKD stage 4 or 5/5D and genotype 1, with 76% of the patients being haemodialysis dependent. After 12 weeks, 99% of patients achieved SVR. Serum creatinine raise and the need for dialysis initiation were similar with the control group (who received placebo) and the frequency of adverse effects was low (most common adverse effects were: headache, nausea, fatigue) [27].

TABLE 4. AASLD recommendations for DAAs therapy in CKD patients [9]

Recommendation for patients with CKD stage ^a	Rating
No dose adjustment in direct-acting antivirals is required when using recommended regimens ^b	I, A or IIa, B ^c

^aChronic kidney disease (CKD) stages: CKD stage 1 – eGFR > 90 ml/min; CKD stage 2 – eGFR 60-89 ml/min; CKD stage 3 – eGFR 30-59 ml/min; CKD stage 4 – eGFR 15-29 ml/min; CKD stage 5 – eGFR < 15 ml/min.

^bRibavirin dose must be reduced in CKD stage 3,4,5. ^cIA – for patients with CKD stage 1,2 and 3; IIa,B for CKD stage 4 and 5.

IMMUNOSUPPRESSIVE THERAPY AND HEPATIC DISEASE

Immunosuppressive therapy must be initiated in patients who have severe complications – RPGN (rapidly progressive glomerulonephritis), severe neuropathy or extensive skin disease and also in nephrotic range proteinuria and/or progressive renal disease and/or cryoglobulinemia flare, before DAAs therapy initiation [28].

Possible therapeutic regimens include:

- Rituximab (375 mg/m² every week for 4 weeks) ± corticotherapy
- Cyclophosphamide (2 mg/kg/day for 2-4 months) + Methylprednisolone 0.5-1g/day, 3 days [29,30].

Previous regimens included a combination between cyclophosphamide and corticosteroids, followed by maintenance therapy with azathioprine, while waiting for a response from antiviral therapy [31]. DAAs have a rapid antiviral effect so the role of immunosuppressants for the treatment of severe glomerular disease must be clarified.

A retrospective study on 105 patients found poor prognosis factors (independent risk factors for death or dialysis initiation) in patients with cryoglobulinemia and renal disease:

- Age > 50 years
- Skin purpura

- Splenomegaly
- Cryocrit level > 10%
- C3 < 54 mg/dl
- Serum creatinine >1.5 mg/dl [33]

TABLE 5. Management of patients with HCV-induced glomerulonephritis [32]

Clinical presentation	Management
Proteinuria <3.5 g/day Stable renal function and/or moderate kidney dysfunction	Antivirals: DAAs Antiproteinuric agents: ACEIs/ARBs Diuretics, antihypertensive agents
Nephrotic syndrome Cryoglobulinemic vasculitis flare RPGN	Immunosuppression: Rituximab, plasma exchange, intravenous steroids, cyclophosphamide Antivirals: DAAs Antiproteinuric agents: ACEIs/ARBs Diuretics, antihypertensive agents

ACEIs: angiotensin-converting enzyme inhibitors;

ARBs: angiotensin-receptor blockers; DAAs: direct acting antiviral agents;

GFR: glomerular filtration rate; RPGN – rapidly progressive glomerulonephritis

When having a patient with hepatitis C virus infection, clinicians must take into account 2 important aspects: hepatotoxicity and viral reactivation due to the same immunosuppressive therapy.

Immunosuppressants can be directly hepatotoxic or they can amplify a preexistent hepatic disease, especially in the situation of a viral hepatitis [34-36]. When hepatic metabolism is altered due to a preexistent hepatic disease, it can lead to higher and more persistent levels of a drug, causing a raise in systemic toxicity and exacerbating hepatic dysfunction.

Higher doses of immunosuppressive therapy (chemotherapeutic doses) associate with impaired liver functional tests in patients with hepatitis C virus, but it can cause problems only in the situation of a decompensated hepatic disease. The actual recommendation is to continue with immunosuppression if there are no severe alterations of liver functional tests [37,38].

The incidence of viral reactivation post immunosuppression is still unknown. Viral replication and liver damage occur less frequently in HCV carriers than in the case of HBV (hepatitis B virus) carriers after withdrawal of immunosuppressive therapy, and hepatitis exacerbation frequency is not as high as expected. There are currently no reliable means of predicting the risk of developing HCV reactivation or the degrees of severity should this occur. Furthermore, whether antiviral prophylaxis prevents HCV reactivation remains unclear [33].

Even if viral replication increases, the cases of severe hepatitis or hepatic decompensation of a preexistent hepatic disease are rare, maybe because

of a less vigorous immune response to viral antigens – which finally induces a higher chronicity rate [28]. Savas et al. demonstrated that HCV reactivation occurred in almost 50% of renal transplant recipients in the first two years after kidney transplant, but patient survival and graft survival were not affected by HCV reactivation [39].

Some of clinicians support the necessity of an antiviral prophylaxis, starting from the idea that during dose tapering or after stopping the treatment, a massive immune response directed against viral antigens can occur, leading to massive hepatic destruction [40].

DAA's are effective and more tolerable than IFN-based regimens and trials of antiviral therapy in patients coinfecting with HIV and HCV or on immunosuppressive therapy for solid organ transplant [41] have demonstrated that treating HCV in immunocompromised patients can be effective in achieving SVR [42], even though this happens at lower rates than in patients with an intact immune system. Colombo et al. reported a 98% SVR in renal transplant recipients treated with sofosbuvir/ledipasvir for 12 weeks or 24 weeks and SVR was not associated with adverse effects or acute rejection [43]. DAAs inhibit viral replication without inducing an additional immune response and can eradicate virus C infection, but it is not clear yet to what extent an intact immune system is necessary for viral eradication with DAAs [44-46].

TABLE 6. Managing HCV during chemotherapy and immunosuppression-AASLD and IDSA recommendations [24]

Monitoring for HCV during chemotherapy and immunosuppression	
NOT RECOMMENDED	Rating
Prospective monitoring for HCV recurrence among patients who achieved SVR and are receiving immunosuppressive drug therapy (systemic corticosteroids, antimetabolites, chemotherapy, biologic agents etc.) is not routinely recommended	III, C

AASLD: American Association for the Study of the Liver;
IDSA: Infectious Diseases Society of America

Kidney transplant recipient is the most studied category of patients with renal disease receiving immunosuppression. KDIGO recommends that all HCV-infected patients who are candidates for kidney transplantation be considered for DAA therapy, either before or after transplantation (1A). It is suggested that all conventional current induction and maintenance immunosuppressive therapy regimens be used in HCV-infected patients (2D), but it is also recommended an ALT measurement monthly for the first 6 months and every 3-6 months, thereafter [5].

Because of the high risk of allograft rejection, interferon-based therapy was indicated after kidney transplantation only when the benefits outweighed the risk (fibrosing cholestatic hepatitis, life-threatening vasculitis), but it was abandoned when the use of DAA became available [47,48].

Cyclophosphamide

Cyclophosphamide is efficient in HCV-associated glomerulopathies because is an agent for inhibition of B lymphocytes and thus cryoglobulin production.

Even though it is metabolized by the liver into his active compound, liver failure due to cyclophosphamide is rare. Navin Pinto et al. showed that genetic polymorphisms in enzymes which metabolize this alkylating agent (cytochrome P450, glutathione S-transferase and aldehyde dehydrogenases) are linked to the efficiency and toxicity of this drug [49]. Three histologic patterns have been described: massive hepatic necrosis with only the reticular framework and sinusoids remaining, diffuse hepatocellular destruction in conjunction with mild fatty infiltration, cytolytic necrosis of perihepatic venous hepatocytes [50,51]. Rarely, case reports described fibrosing cholestatic hepatitis (including progressive forms of liver failure) after the administration of this drug [52,53].

Usually, this alkylating agent can induce hepatotoxicity in a dose dependent manner, but hepatic cytolysis can occur after low-dose intravenous treatment (200 mg) with functional liver tests returning to their normal value after cessation of treatment (although irreversible fulminant hepatic failure and death may emerge as a rare complication) [54].

Most clinicians assume that hepatic failure appears due to an idiosyncratic reaction rather than a direct toxicity reaction [55]. Even though preexisting liver disease has little impact on the hepatotoxicity profile, some recommend to lower the dose with 25% in patients who have a serum bilirubin between 3.1 and 5 mg/dl or AST > 3 x N and not to give cyclophosphamide if serum bilirubin is higher than 5 mg/dl [37].

Mycophenolate mofetil

Mycophenolate mofetil is more selective than cyclophosphamide in inhibiting lymphocyte proliferation and functions and may represent a less toxic alternative for the induction treatment in mixed cryoglobulinemic vasculitis. MMF (mycophenolate mofetil) may also be a safe and effective

maintenance treatment for vasculitis, even in the case of cryoglobulinemic vasculitis (when used as therapy for vasculitic ulcers MMF has a good clinical response and an excellent tolerance) [56].

MMF reduces hepatitis virus C incidence after hepatic transplant and HCV RNA levels in patients with HCV recurrence after hepatic transplant [57], but data showed that it can also favor viral replication when used in renal transplant patients, although there are no convincing data of a specific deleterious effect [58,59]. It also has anti-HCV effect, by decreasing viral load and AST and ALT levels in patients with hepatic transplant, through its ribavirin-like effect (IMPDH inhibitor) [60-62]. *In vitro* studies have shown that MMF suppresses completely viral replication cycle, as evidenced by the lower expression of viral proteins and HCV RNA. It seems that the inhibition was due to the depletion of guanosine, a crucial purine for the synthesis of guanosine triphosphate which is necessary in HCV RNA replication in human hepatic cells [61].

Medina et al. reported the use of MMF to treat 5 patients with SLE (systemic lupus erythematosus) and diffuse proliferative glomerulonephritis associated with HCV infection. All patients had a favorable response evidenced by the reduction of proteinuria (higher than 50% in four of them) with normalization of C3 levels, with no significant adverse effects. This means that MMF may be used in monotherapy and even in association with other drugs, without worsening HCV infection and without major side effects [63].

Azathioprine

Multiple mechanisms of hepatotoxicity have been reported for azathioprine:

- Hypersensitivity [64]
- Cholestasis [65-67]
- Nodular regenerative hyper-plasia [68,69]
- Venocclusive disease [70]
- Peliosis hepatis [71]
- Sinusoidal dilatation [72]
- Hepatocellular lesions
- Mixed lesions

Hepatotoxicity can be an idiosyncratic or a dose-dependent reaction and although rare [73], it has been described more frequently in male patients and in renal transplant recipients and the classic clinical aspect is acute cholestatic hepatitis, although the lesions can be more complex (even asymptomatic patients with raised serum aminotransferase levels) [74,75].

It was assumed that patients who develop a toxic hepatic reaction can transform faster (in a genet-

ically determined manner) azathioprine in 6-MP (6-mercaptopurine).

The variability of clinical manifestations is the expression of different mechanisms of action. 6-mercaptopurine, an azathioprine component, can induce hepatocellular and cholestatic lesions [76], while the other component – 6-thioguanine – can induce veno-occlusive disease [77]. At higher doses, azathioprine promotes an important reduction of glutathione in endothelial sinusoidal cells and in hepatic cells, but in therapeutic doses, cellular oncosis is the mechanism that promotes hepatic lesions. Cellular oncosis is caused by xanthine-oxidase that induces oxidative stress and has glutathione and ATP (adenosine triphosphate) depletion as final result [78].

It is recommended to monitor hepatic profile during treatment with azathioprine to reduce the incidence of hepatic toxicity. A moderate increase of ALT/AST is the equivalent of reversible hepatic lesions and does not impose stopping the treatment, but a severe increase must be followed by a dose reduction by 50% and a close follow-up (even in this setting, serum aminotransferase level returns to normal and clinicians can return to initial dose of immunosuppressant). In icteric patients, it is recommended to stop azathioprine immediately due to a severe potential evolution [79].

Rituximab

Rituximab is a monoclonal antibody against CD20 and depletes B lymphocytes, interferes with cryoglobulin synthesis and with renal deposition of immune complexes, being considered first-line therapy for HCV-associated glomerulonephritis. Nevertheless, the moment when rituximab can be initiated is unknown, just like the doses for the treatment of relapses, meaning that his role as first-line or rescue-line therapy is not yet well defined.

Case reports have shown that symptomatology improves after the 3D regimen (dasabuvir and paritaprevir/ritonavir/ombitasvir) combined with plasmapheresis, corticosteroids and rituximab [80]. Rituximab therapy associated with PegIFN-alfa2b/ribavirin is superior to antiviral therapy with a renal response rate of 81% vs 40% [81].

When compared to cyclophosphamide, rituximab inhibits as efficient as cyclophosphamide the synthesis of immune complexes and cryoglobulins and it does not cause flares of HCV infection – the levels of HCV RNA remaining stable during rituximab treatment [82,83]. Even more, studies showed that depletion of CD20+ B cells in patient with cryoglobulinemia and advanced liver disease, was

followed by cirrhosis syndrome improvement despite the possibility of a transient increases of viremia titers [84,85].

The clinician must take into account the fact that rituximab therapy is associated with a high risk of opportunistic infections (parvovirus B19 [86], CMV (cytomegalovirus) [87], fatal varicella-zoster infection [88] have been reported following rituximab). Also, renal failure (GFR < 60 ml/min), older age (age > 70 years) and simultaneous corticosteroid treatment have been noted as risk factors for rituximab-associated sepsis [89].

Plasmapheresis

Removing immune complexes from circulation through plasmapheresis may retard the accumulation of immune complexes into the kidney. This is efficient in rapidly progressive glomerulonephritis and could be combined with immunosuppressive therapy. The usual dose in the treatment of HCV-induced glomerulonephritis is the exchange of 3 l of plasma 3 times/week.

Because it does not have an effect on the production of cryoglobulins, plasmapheresis induces a temporary remission and it does not have a long-term benefit which means it has to be combined with an immunosuppressant [1].

In cryoglobulinemic flares (especially when associated with severe glomerular lesions), immunosuppressive therapy must be used in acute phase and antiviral therapy with DAAs can be initiated in the same time or after immunosuppression [90,91].

DAAs therapy has high rates of SVR and future studies will establish if this new therapy will reduce the need for immunosuppression in HCV-associated glomerulonephritis.

Corticosteroids

Corticosteroids can be used in renal flares of membranoproliferative glomerulonephritis, but they can increase viral replication and can accelerate hepatic fibrosis by two mechanisms:

- Direct effect on the virus by enhancing viral replication
- Indirect effect due to the suppression of the HCV immune response – which allows viral replication [92].

Henry et al. tested *in vitro* the effects of steroids on HCV replication and showed that at clinically relevant concentration, prednisone and dexamethasone did not enhance, but resulted in a minor reduction of HCV replication (a reduction of relative luciferase activity and a reduction of HCV RNA

levels) [93]. In conclusion, the augmentation of viral replication after a high-dose of steroids might be due to a downregulation of the immune response. A dampened immune response allows HCV to replicate free of a destruction of their host cells. When tapering the dose of immunosuppressants, the immune system is more vigorous in his attempts to kill the virus and this results in an accelerate liver damage [94-96].

High doses of corticosteroids have been associated with the development or exacerbation of non-alcoholic steatohepatitis with elevations in serum aminotransferase levels. Corticosteroids inhibit mitochondrial beta-oxidation and lipid beta-peroxidation enzymes, leading to the accumulation of lipids within hepatocytes and they can also induce de novo fatty acid synthesis by activating lipogenic enzymes – fatty acid synthase, acetyl-CoA carboxylase and 11 beta-HSD1 in the liver [97]. Also, they contribute to the appearance of insulin resistance and hyperinsulinemia and lipogenesis as final process [98,99].

Cyclosporine

Clinicians should take into account that CyA (cyclosporine) undergoes hepatic metabolism and its interaction with the cytochrome P450 system can lead to severe drug – drug interactions and to an increase in CyA levels that can result in a high risk of hepatotoxicity [100,101].

Studies concluded that it has antiviral effect (on HIV, herpes simplex etc.), and Firpi et al. showed that liver transplant recipients who received classic antiviral therapy and immunosuppression with cyclosporine had a higher SVR (46%) compared to the group who received tacrolimus-based therapy who had a 27% rate of SVR [102].

Watashi and colleagues have treated HCV human hepatocytes with HCV+ plasma and evaluated HCV RNA in the control cells and in the cells treated with either CyA or IFN-alfa. The viral titre was high in control cells, while no significant increase was observed in cells treated with CyA or IFN-alfa, suggesting that CyA can also be effective in inhibiting HCV replication in infected hepatocytes [103]. The impaired replication of HCV is not due to cytotoxic effect, because the activity of cyclosporine did not interfere with cell growth.

Ishii et al. conducted an *in vitro* study in which they showed HCV genotype 1b is highly sensitive to cyclosporine, while a genotype 2a replicon – JFH1 was less responsive to cyclosporine (although a high dose of CyA suppressed the replication of

this strain). In the report of Inoue, patients co-treated with IFN and CyA had a higher SVR than those treated with IFN alone [104].

Kakumu et al. suggested that CyA reduces serum aminotransferases levels even in relatively low dose, but did not noted an antiviral effect [105].

Martin et al. also brought contradictory results, showing that recurrence of hepatitis C infection in liver transplant recipients occurred at a greater rate between the 6 and 12-months follow-up in the cyclosporine-treated patients but remained relatively stable for the tacrolimus-treated group. Also, changes in HCV RNA levels were significantly higher at 1, 6 and 12-months post transplantation for patients treated with cyclosporine (median HCV RNA serum levels increased by 18.8 million mEq/ml from baseline in patients treated with CyA and by 4.5million mEq/ml in patients treated with tacrolimus [106].

Cyclosporine can also increase serum alkaline phosphatase, serum aminotransferases and bilirubin levels, generally in the second and the third month of treatment and tend to normalize once the dose of CyA is decreased [107-109]. As for histologic changes, patients can present hypertrophy of the bile ductal epithelium with cytoplasmatic vacuoles and the presence of “foamy” material within the hepatic sinusoids [110].

Severe cases of cholestatic hepatitis secondary to CyA have been described, but they had risk factors as icterus and cholestasis, virus C infection and parenteral nutrition prior to the administration of CyA [111,112].

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The risk of gallstones is also high in patients with CyA maintenance treatment, especially in those who take it for more than 2 years, diabetic patients and renal transplant recipients in whom the risk is almost 30% to form a gallstone [113].

CONCLUSIONS

Autoimmune conditions have a high prevalence nowadays and, among these, HCV-associated glomerulonephritis, but the data about immunosuppressive treatment and antivirals are scarce and clinicians need more evidence-based guidance. When having a patient with hepatitis C infection, the clinicians must take into account two important aspects: immunosuppressive hepatotoxicity and viral reactivation due to the same immunosuppressive therapy.

As for antivirals, with the appearance of DAAs, management of HCV infection changed leading to IFN-free and sometimes RBV-free regimens, even in the case of ESRD.

In conclusion, treatment in this special category of patients must be individualized according to the risk of CKD and ESRD, the risk of viral reactivation and replication due to immunosuppression and the risk of drug adverse effects. We sustain the idea that more studies need to be done in order to better define this population.

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