

## Anti-hepatitis C virus drugs and kidney

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### Abstract

Hepatitis C virus (HCV) mainly targets the liver but can

also induce extrahepatic manifestations. The kidney may be impacted *via* an immune mediated mechanism or a cytopathic effect. HCV patients are clearly at a greater risk of chronic kidney disease (CKD) than uninfected patients are, and the presence of CKD increases mortality. Interferon-based therapies and ribavirin are difficult to manage and are poorly effective in end-stage renal disease and hemodialysis. These patients should be given priority treatment with new direct anti-viral agents (DAAs) while avoiding peginterferon and ribavirin. The first results were convincing. To aid in the correct use of these drugs in patients with renal insufficiency, their pharmacokinetic properties and potential renal toxicity must be known. The renal toxicity of these new drugs was not a safety signal in clinical trials, and the drugs are generally efficient in these frail populations. These drugs are usually well tolerated, but recent cohort studies have demonstrated that these new regimens may be associated with renal side effects, especially when using sofosbuvir combinations. HCV, renal diseases and comorbidities are intimately linked. The close monitoring of renal function is required, particularly for at-risk patients (transplanted, HIV-coinfected, CKD, hypertensive or diabetic patients). New DAA regimens, which will soon be approved, will probably change the landscape.

**Key words:** Nephrotoxicity; Hepatitis C; Direct anti-viral agents; Kidney; End-stage renal disease

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**Core tip:** Hepatitis C patients are clearly at risk of chronic kidney disease (CKD). New direct anti-viral agents (DAAs) with different pharmacokinetic properties are generally efficient in such populations. However, renal toxicity has been described in frail patients such as patients with CKD, transplants and human immunodeficiency virus co-infections under real-life conditions, especially with sofosbuvir combinations. New DAAs, which will be soon approved, will probably change the

landscape favorably. Close monitoring of renal function is required for at-risk patients, but patients without comorbidities are probably at a very low risk of renal toxicity.

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## INTRODUCTION

Hepatitis C virus (HCV) mainly targets the liver but also targets the kidney *via* either an immune mediated mechanism (cryoglobulinemic vasculitis) or a cytopathic effect<sup>[1-3]</sup>.

Epidemiological studies show that the risk of chronic kidney disease (CKD) is 20% higher in HCV patients than in uninfected individuals<sup>[4]</sup>. HCV increases the risk of both end-stage renal disease (ESRD)<sup>[5]</sup> and renal mortality<sup>[6]</sup>. Moreover, patients who are infected with HCV exhibit an increased risk of developing diabetes, high blood pressure and secondary vascular renal diseases<sup>[7]</sup>. Finally, chronic hepatitis C is the most commonly seen viral infection in patients with renal insufficiency<sup>[8]</sup>; its treatment is warranted and remains a great challenge.

Historically, interferon-based therapy was considered nephrotoxic in a dose-dependent or idiosyncratic manner<sup>[9]</sup>. First-generation protease inhibitors (*i.e.*, telaprevir and boceprevir in association with peginterferon and ribavirin) have also been implicated<sup>[10]</sup>, although their role remains controversial<sup>[11]</sup>. Although ribavirin is not nephrotoxic, it accumulates in patients with CKD, and its secondary effects (particularly anemia) are much more severe.

Although new direct anti-viral agents (DAAs) were very well tolerated in phase III trials, recent real-life studies have demonstrated some nephrotoxicity in frail populations that were treated with sofosbuvir-based regimens<sup>[12,13]</sup>.

After a brief review of the pharmacokinetics of anti-HCV drugs, we review their potential renal toxicity and clinical experiences related to the use of these drugs in populations at risk of renal disease.

## PHARMACOKINETICS OF HCV

### TREATMENTS

#### **Treatments that are available in 2016**

The combination of pegylated interferon and ribavirin with or without first-generation protease inhibitors (boceprevir and telaprevir) is no longer used in many developed countries<sup>[14-16]</sup>. However, it may still be relevant in developing countries.

Standard care in countries where DAAs are available is based on the combinations of two or three DAAs from

different families: Second-generation protease inhibitors, NS5B polymerase inhibitors, and NS5A inhibitors. Ribavirin may be added in cirrhotic patients to shorten treatment duration.

All but two DAA phase III studies did not include patients with severe renal insufficiency (4-5 CKD stages)<sup>[17,18]</sup>. Sparse data are thus available, and guidelines recommend that these patients be referred to expert centers<sup>[14]</sup>.

To justify the proper use of HCV treatments in renal insufficiency, the pharmacokinetic properties of these drugs should be remembered.

#### **Pharmacokinetics of interferon, pegylated interferons and ribavirin**

Interferons are natural cytokines. Alpha interferon and its pegylated form are active against viral replication. Pegylation prolongs the half-life of interferon, thus necessitating fewer injections<sup>[19-21]</sup>. The kidney plays a central role in interferon clearance. Interferon is filtered through glomeruli and undergoes lysosomal proteolytic degradation during proximal tubular reabsorption<sup>[22,23]</sup>.

Ribavirin is a guanosine analog that exhibits broad-spectrum activity against DNA and RNA viruses. Its mechanism of action is based on the erroneous incorporation of ribavirin triphosphate into replicating RNA strands, thereby inhibiting chain elongation<sup>[24]</sup>. When used with interferon, ribavirin acts synergistically, preventing relapses and breakthroughs, and remains relevant in the DAA era in special circumstances. The major side effects of ribavirin are hemolytic anemia and teratogenicity. The renal excretion of ribavirin and its metabolites accounts for 40% of its clearance; the remainder is eliminated through the spleen *via* its principal metabolite, ribavirin triphosphate, which is captured in erythrocytes. Based on the product characteristics, the ribavirin area under the concentration curve (AUC) is doubled when calculating estimated glomerular filtration rates (eGFRs) between 30 and 45 mL/min per 1.73 m<sup>2</sup> and is tripled when calculating eGFRs between 13 and 30 mL/min per 1.73 m<sup>2</sup><sup>[25]</sup>.

#### **Pharmacokinetics of DAAs**

**First-generation protease inhibitors:** Telaprevir and boceprevir are significantly high CYP3A4, P-glycoprotein (P-gp) inhibitors and are also OATP1B1/2 and OCT 1 and 2 inhibitors, respectively.

Thus, they interact significantly with calcineurin inhibitors in transplant patients and with some human immunodeficiency virus (HIV)-specific medications, thereby increasing the renal toxicity of these drugs by increasing their exposure<sup>[26,27]</sup>. These drugs are poorly eliminated by the kidney (1% for telaprevir<sup>[28]</sup>, 9% for boceprevir<sup>[29]</sup>). Telaprevir is excreted by the tubular cells through organic cation transporter 2 (OCT2) and presents a risk of interaction with medications such as dolutegravir<sup>[30]</sup>.

**New DAAs:** Most new DAAs are eliminated in the bile, with the exception of sofosbuvir, which is the keystone

of the main approved DAA regimens.

Sofosbuvir weakly inhibits CYP3A4, intestinal P-gp, and BCRP. Seventy-two percent of sofosbuvir is eliminated by the kidney, primarily as its main metabolite GS-331007<sup>[31]</sup>. The mechanism of clearance warrants study, even if it is reasonable to evoke tubular excretion by analogy with HIV or hepatitis B virus (HBV) analogs. GS-331007 AUC is greater than 55%, 88% and 451% in cases of mild, moderate and severe renal insufficiency, respectively. GS-331007 exposure is increased by at least 10 to 20 times in patients with ESRD<sup>[32]</sup>.

**Several DAAs can be used in combination with sofosbuvir:** (1) NS3/4 protease inhibitor: Simeprevir moderately inhibits CYP3A and intestinal P-gp and potentially inhibits OATP1B1 and MRP2. Its urinary excretion is less than 1%<sup>[33]</sup>. On average, the simeprevir AUC is increased by 62% in subjects with severe renal impairment. The drug is not eliminated by dialysis; and (2) NS5A inhibitors: Daclatasvir is a substrate of CYP3A4 and P-gp and moderately inhibits OATP1B1/3 and P-gp. Its excretion in urine is < 1%. In case of severe renal insufficiency, AUC is increased by 27%, but no dose adjustment is needed<sup>[34]</sup>. Ledipasvir is a weak inhibitor of P-gp and BCRP. Its renal excretion is < 1%<sup>[35]</sup>, and its pharmacokinetics are not altered by severe renal impairment<sup>[36]</sup>. Velpatasvir moderately interacts with CYP3A4, CYP2C8, OATP and P-gp<sup>[37]</sup> and is primarily eliminated in the feces (> 99%). The sofosbuvir/velpatasvir combination will be available soon. According to very preliminary data, this combination appears well tolerated in subjects with severe renal impairment. Velpatasvir AUC is approximately 50% higher in these subjects than in subjects with normal function<sup>[38]</sup>.

**Other combinations exist:** (1) paritaprevir/ritonavir (anti-protease inhibitor), ombitasvir (anti-NS5A inhibitor) and dasabuvir (anti-polymerase inhibitor). Paritaprevir/ritonavir is a powerful CYP3A4 inhibitor. Ritonavir is a well-known inhibitor of many renal transporters including OAT1, OAT2, MRP2, MRP4 and MATE1<sup>[39]</sup>. The four-drug combination is a substrate of P-gp and CYP3A4 and is mainly eliminated in the bile<sup>[40,41]</sup>. In case of CKD 1, paritaprevir and dasabuvir AUCs are increased by 20%, and ritonavir AUC is increased by 42%. In patients with CKD 2 and 3, paritaprevir and dasabuvir AUCs are increased by 37% and ritonavir AUC is increased by 80%. In patients with CKD 4, paritaprevir and dasabuvir AUCs are increased by 50%, and ritonavir AUC is increased by 114%. Ombitasvir AUC remains unchanged<sup>[42]</sup>, and (2) grazoprevir and elbasvir: This regimen will be available soon. Both molecules are substrates of CYP3A4, OATP and P-gp<sup>[43]</sup>. Less than 1% of grazoprevir and elbasvir are excreted by the kidney; the AUC<sub>0-24h</sub> values of grazoprevir and elbasvir are higher in subjects with severe renal insufficiency relative to controls [1.65- (1.09, 2.49) and 1.86-fold (1.38, 2.51) (90%CI), respectively]. Drug removal by hemodialysis is negligible<sup>[44]</sup>. Clinical

experience shows that dose adjustment is not needed in the setting of non-dialysis-dependent stage 4-5 CKD and dialysis-dependent stage 5 CKD<sup>[17]</sup>.

## SPECIFIC NEPHROTOXICITY OF HCV DRUGS

### *Interferon or pegylated interferon and ribavirin*

A dose-dependent or idiosyncratic renal toxicity of alpha interferon and pegylated interferon is well established although rare<sup>[45]</sup>. This nephrotoxicity is mostly reported in cases of malignancy<sup>[46,47]</sup>. However, no correlations were found among the occurrence of renal involvement, the type of interferon used, administration route, treatment dosage and duration, and the patient's profile. The histological features are nonspecific and various, mainly involving minimal forms of glomerular damage, including cellular hyperplasia and focal segmental glomerulosclerosis, which are often associated with nephrotic syndrome<sup>[45,48-51]</sup>. Interferon may worsen any pre-existing glomerular lesions<sup>[52]</sup>. Microangiopathic thrombosis has also been described<sup>[53,54]</sup>. More rarely, interstitial fibrosis (usually mild) as well as nonspecific interstitial inflammation and tubular atrophy, and interstitial nephritis associated with nephrotic syndrome<sup>[55]</sup> or acute tubulopathy<sup>[47,56,57]</sup> have been reported.

Proteinuria (usually a self-limited proteinuria that does not exceed 1 g/d) is observed in 15% to 20% of patients taking interferon<sup>[58,59]</sup>. Nevertheless, hepatitis C-associated glomerulonephritis may be cured with alpha interferon-based treatment, independent of SVR<sup>[60]</sup>.

Renal failure generally occurs during the first weeks of treatment and rarely occurs after several months<sup>[61]</sup>.

The involved physiopathological mechanisms are not clear. In a cellular model, Lechner *et al.*<sup>[62]</sup> demonstrated that interferon directly affects tubular barrier function in renal epithelial cells in a reversible time- and dose-dependent manner. More recently, the same team showed that alpha interferon can activate caspase-3, -8 and -9, which favors the apoptosis cascade in renal proximal tubular epithelia. Gresser *et al.*<sup>[63]</sup> showed that the daily administration of interferon to newborn mice can lead to severe glomerulopathy associated with glomerular sclerosis and IgG and C3 deposits<sup>[64]</sup>.

Ribavirin renal toxicity has not been documented and is not probable in monotherapy<sup>[65,66]</sup>. Nevertheless, by analogy with the ribavirin apoptotic activity observed in K562 leukemia cells, potential tubular toxicity has been hypothesized<sup>[65,67]</sup>.

### *New treatments and nephrotoxicity*

**Boceprevir and telaprevir:** The first-generation protease inhibitors boceprevir and telaprevir have been combined with pegylated interferon and ribavirin. No renal side effect was found in phase III studies<sup>[68-74]</sup>, which is consistent with the weak renal clearance of these drugs. Nevertheless, in a large cohort (1486 patients),

Mauss *et al.*<sup>[10]</sup> showed a reversible decrease of eGFR in patients taking telaprevir or boceprevir. Similar reports involving telaprevir therapy confirmed this observation and suggested a link with anemia occurrence<sup>[75-78]</sup>. Recently, Kunze *et al.*<sup>[30]</sup> described competition between telaprevir and OCT2, which interacts with creatinine tubular transport and is involved in proximal tubular secretion. Our team validated this hypothesis with a predictive model suggesting that the clinically observed creatinine increase is not due to renal toxicity of the drug<sup>[11]</sup>. Independent of this pharmacological effect, one of our patients experienced acute renal failure at week 20 of telaprevir treatment. In addition to extra-membranous glomerulonephritis, the renal biopsy showed particularly intense interstitial fibrosis that would exceptionally be described by pegylated interferon and probably implies telaprevir or a combination of telaprevir-pegylated interferon<sup>[3]</sup>.

**New DAAs:** The renal toxicity of new DAA was not a safety signal in phase III clinical trials<sup>[79-83]</sup>; however, most of the included patients presented with eGFR values of greater than 60 mL/min per 1.73 m<sup>2</sup> and few comorbidities. The prescription of sofosbuvir is not desirable for patients with an eGFR of less than 30 mL/min per 1.73 m<sup>2</sup>. In practice, however, half of the daily dose<sup>[84]</sup> or a full dose taken every other day<sup>[85]</sup> was found safe. Various recommendations<sup>[14-16]</sup> specify that renal function should be monitored during treatment with sofosbuvir (grade B). Indeed, on the one hand, the drug is cleared by the kidney; on the other hand, a structural analogy with HBV nucleotide analogs is observed. Therefore, competitive risks with other drugs (antiviral or anti-calcineurins) that are eliminated by the tubule are awaited. In a prospective unselected HCV population, we were unable to find evidence for the induction of subclinical tubulopathy by the antiviral treatment when using tools for the early detection of proximal tubular injury (unpublished data). However, potential proximal tubular toxicity can be hypothesized.

DAAs are usually combined with sofosbuvir, *i.e.*, simeprevir, daclatasvir and ledipasvir do not appear to increase renal risk, although it is difficult to distinguish between the contributions of sofosbuvir and other drugs with which it is combined to the occurrence of renal failure: (1) simeprevir: Renal failure resulting from simeprevir therapy was not found in phase III studies<sup>[86,87]</sup>, except in association with sofosbuvir<sup>[13,88]</sup>; (2) daclatasvir: No renal warning was observed in phase III studies<sup>[89]</sup>, except when daclatasvir was associated with sofosbuvir in liver transplant patients<sup>[90]</sup>; and (3) ledipasvir: One case report suggested possible acute renal toxicity, but this occurred in association with sofosbuvir<sup>[91]</sup>.

Concerning the combination ombitasvir, paritaprevir/ritonavir, dasabuvir, plasma creatinine increase was described in 2 of the 293 patients who had experienced previous interferon-based treatment<sup>[92]</sup>. Other phase III studies did not describe any renal adverse event<sup>[93-96]</sup>.

## EXPERIENCES ON ANTI-HCV THERAPIES IN POPULATIONS AT RENAL RISK

### ESRD and hemodialysis

HCV prevalence is high among patients on long-term dialysis (5% to 10% in Europe and in the United States and 10% to 70% in developing countries)<sup>[97]</sup>. HCV decreases global survival in this population<sup>[98]</sup>.

HCV screening is recommended once yearly in hemodialysis patients. Patients generally present with normal transaminase levels<sup>[99]</sup>, low viral load<sup>[100]</sup>, and moderate fibrosis stage<sup>[8,101,102]</sup>, although fibrosis appears to progress more rapidly in this population. For these reasons, anti-HCV treatment is warranted.

Three meta-analyses of historical treatment with pegylated alpha interferon and ribavirin showed a 40% SVR in ESRD<sup>[103-105]</sup>. The results obtained did not differ between alpha interferon and pegylated alpha interferon<sup>[106]</sup>. Ribavirin is generally contra-indicated in patients with eGFR values of less than 50 mL/min due to the high risk of ribavirin metabolite accumulation in erythrocytes, which increases the amplitude of hemolytic anemia<sup>[24,107]</sup>. However, at minimal doses, ribavirin was used after each dialysis session<sup>[108]</sup> or 5 d per week<sup>[109]</sup>. The erythropoietin doses were usually increased<sup>[109]</sup>.

First-generation protease inhibitors in combination with pegylated interferon and ribavirin gave potentially interesting results<sup>[110-113]</sup>, but the observed high antiviral efficacy was accompanied by numerous serious adverse effects<sup>[112]</sup>.

ESRD and dialysis patients should be given priority treatment with new DAAs while avoiding peginterferon and ribavirin.

The currently available data on the approved DAAs are sparse. The adequate dose of sofosbuvir is unknown, and ribavirin should be avoided (see above).

Small preliminary studies, mainly based on the sofosbuvir/simeprevir combination<sup>[84,114,115]</sup>, have shown a SVR rate of between 87% and 100% in ESRD genotype 1 patients. In a real-life TARGET cohort evaluating a sofosbuvir and simeprevir regimen, similar results were observed, with an increased benefit when adding ribavirin; however, anemia risk was increased<sup>[13]</sup>. In summary, the safety of sofosbuvir in ESRD is unclear, and larger trials are awaited.

Recently, preliminary results of the RUBY-1 trial including 20 patients with CKD 4 renal insufficiency receiving the approved regimen of ombitasvir, paritaprevir/ritonavir, and dasabuvir with (genotype 1a) or without (genotype 1b) ribavirin showed a SVR of 90%; however, ribavirin had to be stopped in 9 of the 13 G1a patients<sup>[18]</sup>.

More recently, elbasvir and grazoprevir were administered together once daily in the largest trial to date (the Phase III C-SURFER study); the trial included 224 ESRD patients, 179 of whom were hemodialysis dependent, and achieved a 99% SVR12 in genotype 1 patients<sup>[17]</sup>. Elbasvir and grazoprevir are expected to be approved shortly.

Thus, two regimens are or will be recommended in genotype 1 patients with severe renal insufficiency: Paritaprevir-ritonavir-ombitasvir-dasabuvir for patients with G1b and grazoprevir-elbasvir for patients with all G1 subtypes.

### **Patients with renal impairment**

In the TARGET cohort, the sofosbuvir/simeprevir combination (with or without ribavirin or pegylated interferon) was found to be efficacious and safe in HCV-infected patients of differing CKD stage. Compared with patients without renal insufficiency, these patients experienced a deterioration of their eGFR (25% with an initial eGFR < 30 mL/min per 1.73 m<sup>2</sup>, 13% with an eGFR of between 31 and 45 mL/min per 1.73 m<sup>2</sup>, and 1% to 2% with an eGFR > 45 mL/min per 1.73 m<sup>2</sup>). These results suggest that sofosbuvir-based treatments used in kidney patients warrant close monitoring<sup>[13]</sup>. In the TARGET cohort, patients with a basal eGFR of less than 30 mL/min per 1.73 m<sup>2</sup> showed a high risk of acute renal insufficiency (25%)<sup>[13]</sup>.

### **Kidney transplantation**

HCV prevalence among kidney transplant patients is approximately 10%, and most of the patients are viremic<sup>[116]</sup>. HCV decreases global survival in this population<sup>[117]</sup>.

HCV also increases sepsis, diabetes, glomerulonephritis and rejection<sup>[102,117-120]</sup>.

Anti-viral treatment is recommended for preventing fibrosis progression, risk of fibrosing cholestatic hepatitis and sepsis. Interferon is no longer recommended in this setting due to the strong risk of rejection<sup>[121]</sup>, although this risk has been shown to be lower than expected<sup>[122,123]</sup>. Moreover, meta-analyses have demonstrated a weak SVR rate (18% to 26.9%) and a high rate of withdrawal: 21.1% to 35% with alpha interferon<sup>[124,125]</sup> and 40.6% with pegylated interferon<sup>[125]</sup>. No data with pegylated interferon and boceprevir or telaprevir-based triple therapy are available. However, the data obtained from liver transplant experience show that it is very difficult to manage drug interactions with calcineurin inhibitors, thus leading to serious adverse events<sup>[26]</sup>.

A few published preliminary studies using sofosbuvir-based combinations showed a SVR > 95%; however, the immunosuppressing drug concentrations varied, a finding that should be studied and monitored<sup>[126-130]</sup>. Liver transplantation experience is more important, and treatment of such patients has shown good results in terms of efficacy, tolerance and medication interactions<sup>[90,131]</sup>.

Recently, the concept of pre-transplant treatment has become preeminent, especially for patients of genotypes 1 and 4, due to the availability of regimens avoiding sofosbuvir<sup>[17]</sup>. However, patients with genotypes 2 and 3 for whom sofosbuvir-based regimens are recommended should be treated after kidney transplantation while awaiting new pangenotypic combinations<sup>[132]</sup>.

### **Liver transplantation**

In the French CUPILT cohort of liver transplant patients who were treated with sofosbuvir and daclatasvir,

37.1% experienced a 25% decrease of GFR during or after treatment; however, in 10.9% of the cases, this GFR decrease was not reversible. The existence of prior kidney disease and fibrosing cholestatic hepatitis were both independent predictors of decreased GFR. The authors emphasized the importance of close renal function monitoring in this population<sup>[12]</sup>. These data were confirmed in an American multicenter study<sup>[133]</sup>. Moreover, patients with fibrosing cholestatic hepatitis who were treated with sofosbuvir, ribavirin and pegylated interferon ( $n = 8$ ) or daclatasvir, sofosbuvir and ribavirin ( $n = 14$ ) experienced high rates of renal failure (4/8 and 7/14, respectively), including 1 with creatinine clearance of less than 30 mL/min per 1.73 m<sup>2</sup><sup>[90]</sup>.

### **Coinfected patients**

In coinfecting patients of the ION-4 study, who were treated with sofosbuvir/ledipasvir, 4 of the 335 patients exhibited worsened renal function (a creatinine increase of 35 μmol/L or more); tenofovir AUC<sub>tau</sub> increased by 20% and 30% in two patients, one patient discontinued tenofovir, and the drug dose was reduced for one patient<sup>[134]</sup>.

Renal function improved in all patients after treatment discontinuation.

### **Particular cases**

**Acute renal insufficiency:** Acute renal insufficiency has mainly been reported in cohorts with high renal risk. Recently, the first case of acute kidney injury, as documented by renal biopsy, was described in a patient receiving sofosbuvir and ledipasvir and suffering from hypertension and diabetes mellitus type 2: The biopsy showed an acute allergic interstitial nephritis with diabetic nephropathy. Corticosteroid therapy was introduced, and this stabilized the renal function<sup>[91]</sup>.

**Adolescents and children:** The pharmacokinetics of new antiviral drugs are not known in this population. To our knowledge, only one study using ledipasvir/sofosbuvir (90/400 mg) in 100 adolescent patients (12 to 17 years old) with HCV genotype 1 for 12 wk resulted in an SVR12 rate of 97%, a similar result to that obtained in adults. Ledipasvir/sofosbuvir was well tolerated with no grade 3-4 adverse events, serious adverse events, or treatment discontinuations due to adverse events<sup>[135]</sup> in particular renal events. In the context of the universal use of new DAAs, a study in children aged 3 to < 12 years is ongoing (ClinicalTrials.gov Identifier: NCT02249182).

In summary, sofosbuvir-based combinations have exhibited renal toxicity in frail patients such as CKD, transplant and HIV co-infected patients under real-life conditions. Real-life studies suggest a risk of eGFR deterioration in patients with previous renal impairment, suggesting that these combinations be used cautiously in this setting including, in particular, diabetes mellitus and hypertension.

Physiopathologically, tubular toxicity can be suggested by structural analogy between this drug and antiretroviral analogs; however, this was not demonstrated in patients

with normal renal function. Nevertheless, these new anti-HCV DAAs appear to act synergistically with drugs that are known to exert a toxic action on the tubule, such as anticalcineurins and tenofovir. Finally, a classic drug-induced renal tubulointerstitial disease of immunological origin has recently been described in at least one documented case with renal biopsy.

New combinations, such as paritaprevir-ritonavir-ombitasvir-dasbuvir for genotype 1b and grazoprevir-elbasvir for all genotype 1 subtypes, show promise in patients with severe renal impairment.

## CONCLUSION

HCV treatment should be offered to all patients with ESRD or kidney transplant candidates, regardless of liver fibrosis stage, due to the intimate link between HCV, renal diseases and comorbidities such as cardiovascular complications and diabetes and because of the impact of HCV on mortality.

There is no clear recommendation for the use of currently approved DAAs in cases of severe renal insufficiency; these drugs may be prescribed under certain conditions, preferably without ribavirin. However, expert opinions are needed.

New DAAs, which will soon be approved, will probably favorably change the landscape.

DAA regimens can present renal side effects, especially sofosbuvir combinations. Close monitoring of renal function is required in at-risk patients comprising patients with CKD, ESRD and hemodialysis, hypertension and diabetes, HIV coinfection, and transplant patients. Current recommendations require the universal monitoring of renal function in patients treated with DAAs. However, patients with none of the above described comorbidities are probably at very low risk of renal toxicity and will no longer require such close monitoring in future.

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