Nefrologia xx (2025) 501349

Sociedad Española de Nefrología

nefrología
Revista de la Sociedad Española de Nefrología
journal homepage: www.revistanefrologia.com

Review

Novel evidence on the management of HCV-associated glomerular disease

Nueva evidencia sobre el manejo de la enfermedad glomerular asociada al VHC

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ARTICLE INFO

Keywords:
Chronic kidney disease
Hepatitis C virus
Glomerular disease
Rituximab

ABSTRACT

Hepatitis C virus infection and chronic kidney disease are major public health issues globally and HCV plays activity in various organs and systems including kidneys. Recent large-scale epidemiological studies have highlighted the negative impact of HCV on the incidence and progression of chronic kidney disease in the adult general population of the western world. In addition, HCV-related glomerular disease is a well-known complication of chronic HCV and novel improvements concerning its management has been achieved. A novel systematic review with meta-analysis reported a strong relationship between HCV infection and higher risk of proteinuria in the general population. Twenty-three studies (n = 198,967 unique patients) were identified and overall effect estimate was significant in cross-sectional (OR, 1.47, 95% CI, 1.3; 1.66) ($P < 0.001$) and longitudinal surveys (HR, 1.79, 95% CI, 1.17; 2.74) ($P < 0.001$). The treatment of HCV-related glomerular disease includes now antiviral (direct-acting antiviral agents, DAAs), immunosuppressive and symptomatic drugs. In addition to selective immunosuppression (rituximab, RTX), various combinations of all-oral interferon-free regimens provided with fast and pangenotypic activity is giving us the possibility to treat patients with HCV-related glomerular disease, with and without kidney impairment, and to obtain some clinical benefit. We have collected by a narrative review of the medical literature a cohort of patients (n = 104) with HCV-related glomerular disease, the frequency of sustained viral response was 91% (90/99); complete or partial clinical response was found in 29% (n = 30) or 42% (n = 43), respectively. Recent evidence from a Spanish multicenter survey (n = 139 patients with HCV-related mixed cryoglobulinemia) suggests that successful antiviral therapy lowers significantly 24-h proteinuria, promotes immunological response and improves kidney/patient survival. In conclusion, HCV-related glomerulonephritis remains a difficult-to-treat disease even though the extensive use of DAAs has changed the natural history of HCV and made this disease uncommon.

Palabras clave:
Enfermedad renal crónica
Virus de la hepatitis C

RESUMEN

La infección por el virus de la hepatitis C y la enfermedad renal crónica son importantes problemas de salud pública a nivel mundial y el VHC actúa en diversos órganos y sistemas, incluidos los riñones. Recientes estudios epidemiológicos a gran escala han destacado el impacto negativo del VHC en la incidencia y

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; BCV, boceprevir; CI, confidence intervals; CKD, chronic kidney disease; CC, case–control; CS, cross-sectional; CVD, cardiovascular disease; DAAs, direct-acting antiviral agents; DCV, daclatasvir; DGS, diabetic glomerulosclerosis; DM, diabetes mellitus; 3D, paritaprevir/ritonavir–ombitasvir; EBR, elbasvir; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GZR, grazoprevir; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, haemodialysis; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon; LDV, ledipasvir; KDIGO, kidney disease: improving global outcomes; KT, kidney transplant; MCS, mixed cryoglobulinemia syndrome; MPGN, membrano-proliferative glomerulonephritis; NR, not reported; OR, odds ratio; peg-IFN, pegylated interferon; RBV, ribavirin; RR, relative risk; RRT, renal replacement therapy; RT, renal transplant; RTX, rituximab; SAEs, serious adverse events; SIM, simeprevir; SOF, sofosbuvir; TVR, telaprevir; UACR, urine albumin/creatinine ratio.

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https://doi.org/10.1016/j.nefro.2025.501349
Received 5 December 2024; Accepted 6 May 2025
Available online xxx

Please cite this article in press as: F. Fabrizi, M.F. Donato, C.M. Alfieri, et al., Novel evidence on the management of HCV-associated glomerular disease, Nefrologia, https://doi.org/10.1016/j.nefro.2025.501349

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progresión de la enfermedad renal crónica en la población general adulta del mundo occidental. Además, la enfermedad glomerular relacionada con el VHC es una complicación bien conocida del VHC crónico y se han logrado nuevas mejoras en cuanto a su tratamiento. Una nueva revisión sistemática con metanálisis informó una fuerte relación entre la infección por VHC y un mayor riesgo de proteinuria en la población general. Se identificaron veintitrés estudios (n = 198 967 pacientes únicos) y la estimación del efecto general fue significativa en las encuestas transversales (OR: 1,47; IC del 95%: 1,3; 1,66) (P < 0.001) y longitudinales (HR: 1,79; IC del 95%: 1,17; 2,74) (P < 0,001). El tratamiento de la enfermedad glomerular relacionada con el VHC incluye ahora fármacos antivirales (agentes antivirales de acción directa, AAD), inmunosupresores y sintomáticos. Además de la inmunosupresión selectiva (rituximab, RTX), diversas combinaciones de regímenes totalmente orales libres de interferón, con actividad rápida y pangenotípica, nos brindan la posibilidad de tratar a pacientes con enfermedad glomerular relacionada con el VHC, con y sin insuficiencia renal, y obtener beneficios clínicos. Hemos recopilado mediante una revisión narrativa de la literatura médica una cohorte de pacientes (n = 104) con enfermedad glomerular relacionada con el VHC, la frecuencia de respuesta viral sostenida fue del 91% (90/99); se encontró respuesta clínica completa o parcial en el 29% (n = 30) o 42% (n = 43), respectivamente. Evidencia reciente de una encuesta multicéntrica española (n = 139 pacientes con crioglobulinemia mixta relacionada con VHC) sugiere que la terapia antiviral exitosa reduce significativamente la proteinuria de 24 horas, promueve la respuesta inmunológica y mejora la supervivencia del riñón y del paciente. En conclusión, la glomerulonefritis relacionada con el VHC sigue siendo una enfermedad difícil de tratar, aunque el uso extensivo de AAD ha cambiado la historia natural del VHC y ha hecho que esta enfermedad sea poco común.

Introduction

It has been recently calculated that HCV is a major health issue and the natural history of HCV infection includes chronic hepatitis, cirrhosis, hepatocellular carcinoma and hepatocellular failure.[1] Novel evidence suggests the notion that HCV plays a consistent activity on numerous tissues and organs; HCV has been implicated in derangements of multiple organs systems including cardiovascular, muscular, nervous, ocular, respiratory, skeletal, cutaneous, and urinary systems.[1] The lymphotropic activity of HCV is well known and lymphoma or mixed cryoglobulinemia are associated with HCV infection. An important target of the extra-hepatic manifestations of HCV is kidney and a consistent relationship between HCV and CKD has been mentioned. The link between CKD and HCV infection is bi-directional and HCV is both a cause and consequence of chronic kidney disease.[1]

HCV and CKD are major public health issues all over the world, according to the Global Burden of Diseases Study 2019 there were total 3.16 million deaths and 76.5 million disability-adjusted life years (DALYs) attributable to kidney dysfunction (KD) (2019 year), increased by 101.1% and 81.7% compared with that in 1990, respectively.[2] The 2024 report from the World Health Organization shows that an estimated 50 million people have chronic hepatitis C virus infection with about 1.0 million new infections occurring per year.[3] In addition, improved data from 187 countries demonstrate that the estimated number of deaths from viral hepatitis increased from 1.1 million deaths in 2019 to 1.3 million in 2022.[3] Hepatitis B caused 83% of these deaths and hepatitis C 17%. DAAs can cure more than 95% of patients with HCV infection, but access to diagnosis and treatment is low. There is now no effective vaccine against hepatitis C.[3]

The current prevalence of chronic kidney disease cannot be completely explained by conventional risk factors such as comorbidities (arterial hypertension, diabetes and aging, among others) or lifestyle factors (smoke, overweight, etc.); additional agents have been mentioned such as positive family history of CKD[4] or viral hepatitis (mostly, HBV and HCV).[1] We performed a systematic review of the published medical literature to assess whether positive HCV serologic status is related with greater rate of proteinuria in the adult general population. Twenty-three studies (n = 198,967 unique patients) were identified and separate meta-analyses were made according to the study design. Overall effect estimate was significant in cross-sectional (OR, 1.47, 95% CI, 1.3; 1.66) ($P < 0.001$) and obvious between-study heterogeneity was observed (Q value by Chi-squared [χ^2] test 27.3, $P = 0.02$). The risk of proteinuria after exposure to HCV was also consistent among longitudinal surveys (HR, 1.79, 95% CI, 1.17; 2.74) ($P < 0.001$) and between-study heterogeneity occurred (Q value, 27.82 by χ^2 test, $P = 0.0001$).[5] We concluded that an important relationship between HCV infection and higher risk of proteinuria in the general population exists.

Several causes have been advocated to explain the increased risk of proteinuria in individuals with HCV exposure. Although chronic HCV infection is associated with tubulo-interstitial damage, the most common type of HCV-associated kidney damage is glomerular disease and an association between HCV infection and glomerular disease has been observed in native kidneys and after solid organ transplant.[1] A variety of glomerular diseases have been identified in patients with exposure to HCV (Fig. 1). The most frequent HCV-related glomerular disease is immune complex-mediated membrano-proliferative glomerulonephritis, usually reflecting the presence of type II cryoglobulinemia (Fig. 2). Cases of HCV-associated MPGN without cryoglobulinemia have not infrequently been reported.[1]

The recent work of many investigators on these issues has led us to summarize again the scientific information concerning HCV-associated glomerular disease. The most recent evidence has been appropriately highlighted.

HCV-associated glomerular disease: epidemiology

Some evidence regarding the frequency of HCV-related glomerular disease have been recorded. Initially, this topic was addressed by El-Serag et al.[6] They adopted the computerized databases of the Department of Veteran Affairs and conducted a hospital-based case–control study. They evaluated all cases of HCV-infected patients hospitalized during 1992–1999 (n = 34,204) and randomly selected HCV-negative control individuals (n = 136,816) (matched with cases on the year of admission). Several disorders including kidneys (glomerulonephritis), skin (porphyria cutanea tarda, vitiligo, and lichen planus), hematologic (cryoglobulins, lymphoma), endocrine (diabetes, thyroiditis) and rheumatologic (Sjogren's syndrome) were considered. A higher frequency of membrano-proliferative glomerulonephritis (0.36% *vs.* 0.05%, $P < 0.0001$) but not membranous nephropathy (0.33% *vs.* 0.19%, $P < 0.86$) was observed among US male veterans with HCV infection.

More recently, Moorman et al.[7] performed a population-based prospective observational cohort study at four large health systems in the US (Chronic Hepatitis Cohort Study, CHeCS); the frequency of cryoglobulinemia and nephrotic syndrome was 0.9% (n = 50) and 0.3% (n = 19), respectively, among HCV RNA positive patients

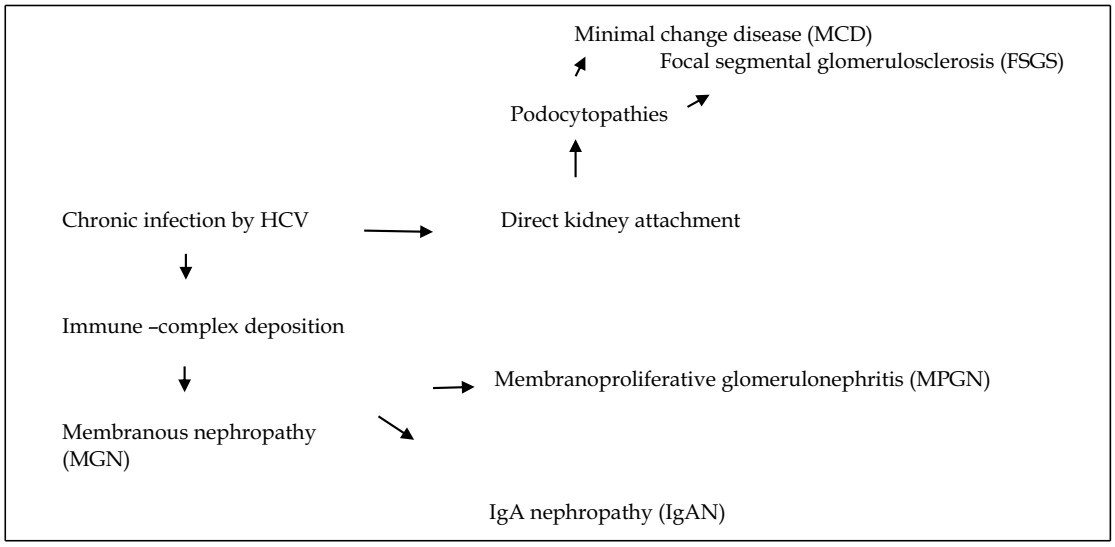

Fig. 1. Glomerular manifestations of chronic HCV infection.

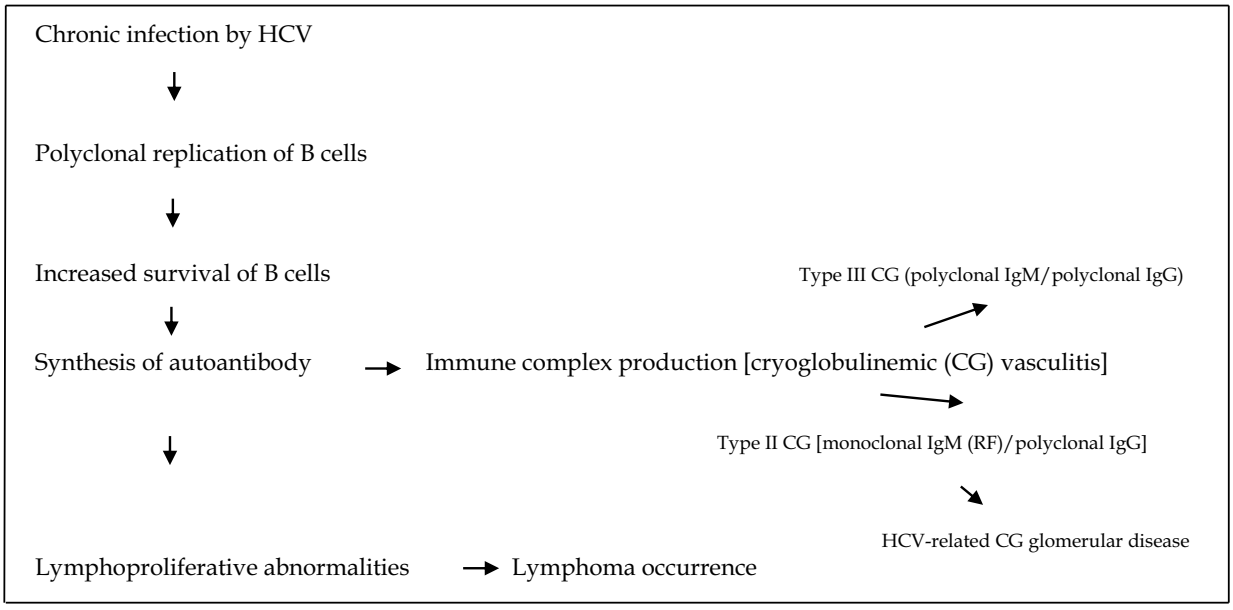

Fig. 2. Development of HCV-related CG vasculitis and glomerular disease.

(n = 5722). CHeCS was a 'real world' survey showing a rate of advanced CKD (CKD stage 4–5) of 2.3% (133/5722). There were 1788 (31.2%) patients and 3851 (67.3%) with eGFR 30–80 ml/min/1.73 m^2 and eGFR >80 ml/min/1.73 m^2, respectively.

Tong and Spradling[8] worked on hospitalization data (2002–2011) from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project. They found that during the study period, the estimated number of hospitalizations among persons with HCV increased to 1,178,633 individuals in 2010–2011. The authors evaluated the frequency of selected health conditions among hospitalized persons (aged, 45–64 years) according to HCV status. The estimated number of hospitalizations with and without HCV was 932,141 and 18,626,828 respectively. Tong and coworkers observed that the prevalence of cryoglobulinemia and nephrotic syndrome/membrano-proliferative GN among hospitalizations with HCV infection was greater than without HCV, 0.33 (0.03%) *vs.* 0.008 (0.01%) ($P < 0.001$) and 0.38 (0.02%) *vs.* 0.16 (0.004%) ($P < 0.001$), respectively. Overall, the frequency of cryoglobulinemia and nephrotic syndrome/membrano-proliferative GN among hospitalization with HCV was low (<0.5%). An important limitation was that the study was limited to hospitalized patients, whose comorbidity profiles could differ from ambulatory populations.

El-Serag et al.[9] made another retrospective cohort study at the Department of Veteran Affairs (46,930 patients with detectable HCV RNA in serum) who received a first course of DAAs, the baseline frequency of GN (using the ICD9-10 code) was 2.6%. These investigators compared the frequency of mixed cryoglobulinemia and GN among patients who obtained SVR in comparison with those who did not, the prevalence was consistently reduced after therapy with DAAs [aHR = 0.23, 95% CI 0.10; 0.56 ($P = 0.0012$) and aHR = 0.61, 95% CI, 0.41; 0.90 ($P < 0.01$) respectively], according to a multivariate fully-adjusted model.

The histology of HCV-associated kidney disease

An important report regarding the histology of HCV-associated kidney disease has been recently published by Guo et al.[10] at the

Vanderbilt University Medical Center (VUMC), USA. A total of 9836 native kidney biopsy samples were addressed (2007–2016), 273 (2.8%) specimens were from patients with HCV infection. Three groups of kidney diseases among HCV positive patients were found; HCV-associated glomerular disease (n = 115), other immune complex-mediated glomerular diseases (n = 31), and non-immune complex-mediated kidney diseases (n = 127). Five histological patterns of glomerular injury were categorized in the subset of HCV-associated glomerular diseases: focal proliferative glomerulonephritis (n = 6); diffuse mesangial proliferative pattern (n = 58); diffuse membrano-proliferative pattern (n = 33); proliferative glomerulonephritis with crescentic lesions (n = 9); and membranous pattern (n = 9). Non-immune complex-mediated kidney disease in HCV positive patients (n = 127) included diabetic nephropathy (n = 54), nephrosclerosis (n = 34), and interstitial nephritis (n = 7). Of note, the authors did not find significant differences in the histological spectrum of kidney disease in the more recent era compared with the pre-DAA era. Kidney biopsy in HCV-infected patients with clinical evidence of glomerular disease is strongly encouraged.

Kung et al.[11] at the Cedars-Sinai Medical Center in NYC (USA) evaluated a total of 310 kidney biopsies from patients with DM and HCV. This represents 0.68% (116/17,134) of post-DAA era biopsies in comparison with 1.34% (194/14,513) of all kidney biopsies in the pre-DAA era ($P < 0.0001$). Two hundred forty-five biopsies (154 pre-DAA, 91 post-DAA) met inclusion criteria. The investigators found that the adoption of DAAs changed dramatically the histology of HCV-related glomerular disease among diabetics. These authors observed numerous changes after introduction of DAAs; the number of kidney biopsies lowered after adoption of therapy with DAAs (0.68% *vs.* 1.34%, $P < 0.0001$); a lower number of kidney biopsies with MPGN occurred (2% *vs.* 10%, $P < 0.02$), a greater number of kidney biopsies with advanced diabetic glomerulosclerosis (DGS) (85% *vs.* 61%, $P = 0.0002$), a more number of biopsies with overall vascular sclerosis (2.1 ± 0.9 *vs.* 1.6 ± 0.8, $P < 0.0001$) was found. Also, non-collapsing FSGS was more frequent after introduction of DAAs (57% *vs.* 31%, $P < 0.0001$). Kung et al. concluded that DAAs reduced active HCV infection and this finding translated into more advanced disease unrelated to HCV [vascular sclerosis (VS), diabetic glomerulosclerosis (DGS), interstitial fibrosis/tubular atrophy (IFTA)]. On the contrary, the incidence of MPGN decreased.

HCV promotes the incidence of chronic kidney disease: an update

The relationship between HCV and chronic kidney disease is complex and has been evaluated in many studies conducted in the past fifteen years.[1] Patients on maintenance dialysis are at risk for HCV infection due to nosocomial transmission of HCV and show large frequency of anti-HCV antibody; however, a large frequency of HCV infection has been also observed in patients with CKD at pre-dialysis stage. This suggests a role of HCV in the incidence and progression of HCV in the general population of western world. Recently, additional studies have been made on this point; this prompted Nawaz et al.[12] to address again the evidence. These authors carried out a systematic review with meta-analysis of clinical studies (n = 12; n = 605,858 unique patients). According to the subset of longitudinal studies (n = 6; n = 347,120 unique patients), they found a significant association between positive anti-HCV serologic status and greater incidence of CKD. The summary estimate for adjusted hazard ratio was 1.21 (95% confidence interval 1.13; 1.29, $P = 0.001$). Between-study heterogeneity was found (P value by Q test <0.001). It is worthwhile to note that the risk of occurrence of CKD associated with HCV (in the subset of Asian patients) was 1.70 (95% CI, 1.4; 2.0) and no heterogeneity was recorded (P value by Q test = 0.6).

Antiviral therapy of HCV prevents chronic kidney disease

Some authors found that viral eradication after antiviral therapy towards HCV decreases the risk of CKD by around 30%. Park et al.[13] conducted a retrospective cohort analysis of the Truven Health MarketScan Database (2008–2015) in the USA; there were 56,448 HCV positive patients and 169,344 propensity score-matched (1:3) sero-negative patients. Within the group of HCV positive patients (n = 56,448) many received antiviral therapy (n = 55,818). Of these patients, 6.6% (n = 3666), 6.3% (n = 3534), and 8.3% (n = 4628) patients received either interferon-based dual, triple, or all-oral direct-acting antiviral agent therapy, respectively, whereas 79% of patients did not receive any HCV treatment. In a multivariate time-varying Cox regression model, HCV-infected patients had a 27% increased risk of CKD compared with non-HCV patients (hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.18–1.37). Among HCV patients, individuals who received the minimally effective HCV treatment for dual, triple, or all-oral therapy had a 30% decreased risk of developing CKD (HR, 0.70; 95% CI, 0.55–0.88). However, the authors noted that the association between decreased risk of CKD and antiviral therapy of HCV was not significant for all-oral therapy.

Sise et al.[14] performed a retrospective observational cohort study including 1178 patients who received DAAs from 2013 to 2017. The mean age of the study group was 57 ± 11 years, there were 754 males (64%), 534 (45.3%) cirrhotics, 306 diabetics (26%). In patients with eGFR less than 60 ml/min/1.73 m^2, the annual decline in eGFR in the three years prior to treatment was −5.98 ml/min/year (95% confidence interval −7.30 to −4.67) and improved to −1.32 ml/min/year (95% confidence interval −4.50 to 1.88) after DAA therapy. In patients with eGFR greater than 60 ml/min/1.73 m^2 the annual decline in eGFR in the three years prior to treatment was −1.43 ml/min/year (95% confidence interval −1.78 to −1.08) and after DAA therapy was −2.32 ml/min/year (95% confidence interval −3.36 to −1.03). In other words, patients with eGFR >60 ml/min/1.73 m^2 at baseline had a clinical but statistically significant increase in eGFR loss per year when averaged over 3 years before and after DAAs. The authors carried out a sensitivity analysis including eGFRs with 1 year before and after therapy with DAAs, and no change in eGFR in this patient subset was recorded. The conclusion of the authors was that DAA therapy for HCV infection may slow CKD progression.

Of note, in nondiabetic patients (n = 27), the albuminuria improved after DAAs ($P < 0.025$ for the difference in the natural log of proteinuria). In diabetic patients (n = 80), the average albuminuria remained stable. These results suggest that DAA therapy for HCV infection reduces albuminuria in patients with DM and HCV.

Antiviral treatment of HCV and kidney dysfunction

The standard of care for HCV-associated glomerular disease is now given by IFN-sparing combinations of DAAs. These regimens are effective and safe even in patients with advanced CKD with a frequency of serious AEs less than 10%. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have issued clinical guidelines in order to suggest appropriate combinations of DAAs in patients with kidney dysfunction.[15] These guidelines have been updated recently (October 2022). All patients with eGFR ≥30 ml/min/1.73 m^2 can be treated with any licensed DAA-based regimen. Table 1 reports some DAA-based combinations that have been recommended for patients with advanced CKD (CKD stage 4–5).

Treatment of HCV-related glomerular disease: historical perspective

The discovery of HCV and an improved understanding of the pathophysiology of disease have given the possibility to control HCV-

Table 1
Some antiviral regimens based on DAAs currently available for treatment of HCV in advanced CKD (CKD stage 4–5).[a]

Glecaprevir (300 mg)/pibrentasvir (120 mg)	8 weeks
Ledispavir (90 mg)/sofosbuvir (400 mg)	12 weeks
Sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
Elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks

No dose adjustment in direct-acting antiviral is required when using recommended regimens.

[a] Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 ml/min); 2 = mild CKD (eGFR 60–89 ml/min); 3 = moderate CKD (eGFR 30–59 ml/min); 4 = severe CKD (eGFR 15–29 ml/min); 5 = end-stage CKD (eGFR <15 ml/min).

associated glomerular disease with various strategies. First, antiviral agents have been given to target the underlying infection that is considered the driver of immune complex formation and consequent glomerular disease; second, non-selective immunosuppressive agents have been administered to lower the inflammation at glomerular level; third, selective immunosuppressive therapy depletes B cells and reduce the synthesis of cryoglobulins.

The role of antiviral therapy in the management of HCV-related cryoglobulinemic glomerulonephritis has been already reviewed. Antiviral therapy has been adopted to obtain clearance of HCV from serum and lower kidney injury. Johnson et al.[16] were the first authors who adopted antiviral therapy (interferon alpha) and observed reduction in proteinuria and improvement of kidney function in association with HCV RNA clearance in patients with HCV-related cryoglobulinemic glomerular disease. These authors did not give information on SVR (sustained virological response, HCV RNA clearance from serum during antiviral therapy which persists at least 6 months after completion of antiviral therapy) which was the standard of cure of antiviral therapy towards hepatitis C.

The adoption of antiviral therapy in the management of HCV-related cryoglobulinemic glomerular disease is based on many anecdotal reports and small-sized observational studies. Initially, monotherapy with conventional therapy was used but afterwards combined antiviral therapy (interferon plus ribavirin) was prescribed. We suggest IFN-free/RBV-free antiviral regimens for the treatment of HCV-related glomerular disease in order to avoid the toxicity induced by IFN and/or RBV. These drugs, indeed, show increased toxicity in patients with reduced glomerular filtration rate.

In 2014 there was the publication of the first report on DAA use[17] – the authors administered the NS3-4A proteases inhibitors (boceprevir and telaprevir) in HCV-associated glomerulopathy, and clinical improvement after HCV eradication was described. Nevertheless, these first-generation DAAs were always given in association with peg-IFN/RBV and used for long periods, triggering serious side effects, mainly severe anemia.

Antiviral treatment of HCV-related glomerular disease: current evidence (1)

In 2016, Saadoun et al. reported on some patients with HCV-associated glomerulopathy treated for 24 weeks with a truly IFN-free regimen (SOF and RBV).[18] They included 24 patients with HCV-cryoglobulinemic vasculitis, five having kidney involvement. Four of these had a renal biopsy showing membrano-proliferative GN. All patients achieved SVR. Kidney disease improved in four out of five (80%) patients. Haematuria occurred in four of five (80%) at diagnosis and disappeared in all cases at week 24. Daily proteinuria decreased from 1.09 (0.6–2.4) to 0.17 (0.07–0.25) g. The median creatinine level was 89 μmol/l (80–163) at baseline and 85 μmol/l (78–146) at week 24. IFN-free antiviral regimens with DAAs are now the standard of care for HCV therapy in the western world. As listed in Table 2, additional studies[18–33] based on IFN-free regimens have been published regarding the treatment of HCV-related glomerular disease; it is an uncommon disease and this hampered the publication of trials with appropriate size and follow-up. According to a narrative review of the medical literature (Table 2) collecting a cohort (n = 104) of patients with HCV-associated glomerulonephritis, the frequency of sustained viral response was 91% (90/99). Complete or partial clinical response was 29% (30/102) or 42% (43/102), respectively.

The introduction of IFN-sparing regimens has resulted in a notable advance in the clinical management of these patients. IFN-based antiviral therapies were frequently toxic, particularly in patients with reduced glomerular filtration rates. Patients with kidney impairment are frequently anemic at baseline and this supports the toxicity (hemolytic anemia) related to ribavirin adoption. The recent introduction of DAAs provided with fast action, lowered treatment duration, and reduced costs is improving the management of HCV-related glomerular disease (Table 1) with or without kidney impairment. It is a disease that frequently affects patients who are not very young and with multiple comorbidities linked to HCV infection. Therefore, they are patients subjected to multiple therapies and drug interactions should not be underestimated.

Antiviral treatment of HCV-related glomerular disease: current evidence (2)

The largest survey on this point is the RENALCRYOGLOBULINEMIC study – it is an observational multicentre cohort study of 139 HCV positive patients with MCS from 14 Spanish centres.[34] Patients were divided into three groups based on the treatment received: treatment with DAAs (n = 100), treatment with interferon (IFN) ± ribavirin (RBV) (n = 24) and no treatment (n = 15). Patients were followed up for a median duration of 138 months (interquartile range 70–251). At baseline, 65 patients have glomerular disease confirmed by kidney biopsy (MPGN pattern) and 37 of them underwent DAAs treatment. The authors observed no change in eGFR at baseline *vs*. end of follow-up, regardless of whether patients had been treated with DAAs, IFN ± RBV or had not been treated. There was a decrease in 24-h proteinuria (in patients treated with DAAs) at the end of treatment (1–3 g/day *vs*. 2.4 g/day at baseline, $P < 0.003$) and at the end of follow-up (0.9 g/day *vs*. 2.4 g/day at baseline, $P < 0.001$). In the subset of patients treated with IFN/RBV, there was a reduction of 24-h proteinuria without statistical power. In terms of virological response, the RENALCRYOGLOBULINEMIC study reported that 98% of patients treated with DAAs achieved SVR compared with 43.5% of patients who received IFN ± RBV regimens.

Renal survival was greater in patients treated with DAAs (log rank 19.718; $P < 0.001$). Using the Cox regression model adjusted for baseline eGFR and proteinuria, patients treated with DAAs had a lower risk for duplication on baseline creatinine values or for dependence on renal replacement therapy (hazard ratio [HR] 0.10 [95% confidence interval (CI) 0.04–0.33; $P < 0.001$). Treatment with DAAs reduced the risk for a kidney event by 90%.[34]

According to the RENALCRYOGLOBULINEMIC study, there were 10 (66.6%) deaths among untreated patients, 9 (37.5%) among those treated with IFN ± RBV and 4 (4%) among those treated with DAAs. Therefore, the death rate in patients treated with DAAs was lower compared with historical controls treated with IFN ± RBV, and lower than in untreated patients (log rank 54.507; $P < 0.001$). Using the Cox regression model adjusted for age, baseline eGFR and proteinuria, patients treated with DAAs had lower mortality [HR 0.12 (95% CI 0.04–0.40); $P < 0.001$]. The conclusion of Perez de José was that treatment with DAAs reduced mortality by 88%.[34]

In patients treated with DAAs, cryocrit percentages at the end of treatment (1.7 ± 2%) and at the end of follow-up (0.7 ± 1.8%) were significantly decreased ($P < 0.001$) compared with pre-treatment levels (5 ± 4.4%). In patients treated with DAAs, C_3 and C_4 levels increased significantly at treatment cessation compared with pre-

Table 2
Viral and clinical response after antiviral therapy with DAAs in patients with HCV-associated GN.

	DAAs	SVR12	Complete clinical response	Partial clinical response	Concomitant IS
Cornella S, et al. (2015) ($n = 5$)	IFN + RBV + BCV/TVR ($n = 2$) IFN/RBV + SOF ($n = 3$)	5 (100%)	2/3 (66%)	0/3	2
Saadoun D, et al. (2015) ($n = 7$)	IFN + RBV + BCV/TVR	NA	5 (71%)	2 (29%)	4 (57%)
Gragnani L, et al. 2016 ($n = 4$)	SOF-based regimen	4 (100%)	3 (75%)	1 (25%)	1 (25%)
Saadoun D, et al. (2016) ($n = 5$)	SOF + RBV	4 (80%)	0	4 (80%)	3 (60%)
Sollima S, et al. (2016) ($n = 5$)	SOF + RBV SOF + DCV SOF + SIM 3D	5 (100%)	0	1 (20%)	0
Sise M, et al. ($n = 7$)	SOF + SIM ($n = 6$) SOF + RBV ($n = 1$)	6 (86%)	3 (43%)	4 (57%)	2 (29%)
Emery J, et al. (2017) ($n = 10$)	SOF + RBV SOF + SIM SOF + LDV + RBV 3D + RBV	7 (70%)	2 (20%)	2 (20%)	4 (40%)
Saadoun D, et al. (2017) ($n = 5$)	SOF + DCV	5 (100%)	4 (80%)	1 (20%)	NA
Bonacci M, et al. (2018) ($n = 9$)	SOF + RBV 3D + RBV SIM + DCV GZR + EBR peg-IFN + DAAs	9 (100%)	6 (67%)	3 (33%)	5 (55%)
Fabrizi F, et al. (2018) ($n = 13$)	SOF + RBV ($n = 6$) 3D + RBV ($n = 4$) SOF + LDV ($n = 1$) SOF + DCV + RBV ($n = 2$)	13 (100%)	3 (23%)	7 (54%)	9 (69%)
Hassan A, et al. (2018) ($n = 7$)	SOF + DCV	7 (100%)	0	5 (71.4%)	0
Lauletta G, et al. (2018) ($n = 4$)	SOF + RBV 3D + DSV + RBV SOF/LDV SOF/DCV	4 (100%)	0	3 (75%)	0
Obrisca B, et al. (2019) ($n = 9$)	3D	9 (100%)	2 (23%)	1 (10%)	6 (67%)
Sise M, et al. (2020) ($n = 10$)	SOF/LDV	8 (80%)	0	5 (50%)	0
Arruda R, et al. (2021) ($n = 2$)	SOF + SIM	2 (100%)	0	2 (100%)	2 (100%)
Abdelhamid W, et al. (2021) ($n = 2$)	SOF + DCV + RBV 3D + RBV	2 (100%)	0	2 (100%)	2 (100%)

Abbreviations: BCV: boceprevir; DCV: daclatasvir; 3D: paritaprevir/ritonavir–ombitasvir; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; IFN: standard interferon; peg-IFN: pegylated interferon; RBV: ribavirin; SIM: simeprevir; SOF: sofosbuvir; TVR: telaprevir.

treatment levels [C_3 levels (baseline) 32 ± 41 *vs*. 101 ± 30 mg/dL, respectively, $P < 0.001$; C_4 levels (baseline) 5 ± 6 *vs*. 14 ± 18 mg/dL, respectively, $P < 0.001$] and at the end of follow-up compared with pre-treatment levels [C_3 levels (baseline) 32 ± 41 *vs*. 100 ± 24 mg/dL, $P < 0.001$; C_4 levels (baseline) 5 ± 6 *vs*. 20 ± 24 mg/dL, $P < 0.001$)]. No significant changes in cryocrit percentage and C_3 and C_4 levels were observed in patients treated with IFN ± RBV.[34]

The RENALCRYOGLOBULINEMIC study offers a piece of solid research but has various shortcomings including the limited size of the control groups (no treatment, or IFN ± RBV treatment, respectively), the kidney histology remains unclear, the information on concomitant immunosuppression is not satisfactory.

Algorithm-based treatment of HCV-related glomerular disease

Fig. 3 reports the management of HCV-related glomerular disease; it is based on the clinical manifestations of glomerular disease. Patients having severe glomerular injury or a cryoglobulinemic flare induced by HCV infection should be given immunosuppressive therapy (rituximab is the first-line drug) with or without plasma exchange. Treatment with DAAs is recommended once the acute phase is successfully managed. In the case of mild or moderate HCV-associated glomerular disease (in short, patients with stable kidney function and/or non-nephrotic proteinuria) DAAs should be administered. Patients with HCV-related glomerular disease showing intolerance or resistance to DAAs should be given immunosuppressive therapy. All patients with HCV-related glomerular disease should receive angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers with the aim to obtain maximum antiproteinuric action.

Treatment of HCV-related glomerular disease and rituximab

The first-line immunosuppressive medication for HCV-related glomerular disease is actually RTX, a chimeric murine-human monoclonal antibody. Rituximab selectively targets CD20 that is widely expressed among B-cell-lineage cells, except for plasmablasts and plasma cells. Thus, RTX deletes IgM production and cryoglobulins.

A very long term prospective single-center open trial was conducted to evaluate the efficacy and safety of RTX in patients with cryoglobulinemic vasculitis (many of them having cryoglobulinemic glomerular disease).[35] The authors adopted the so-called '4 plus 2 protocol'; RTX [375 mg/m^2 on days 1, 8, 15, and 22, followed by

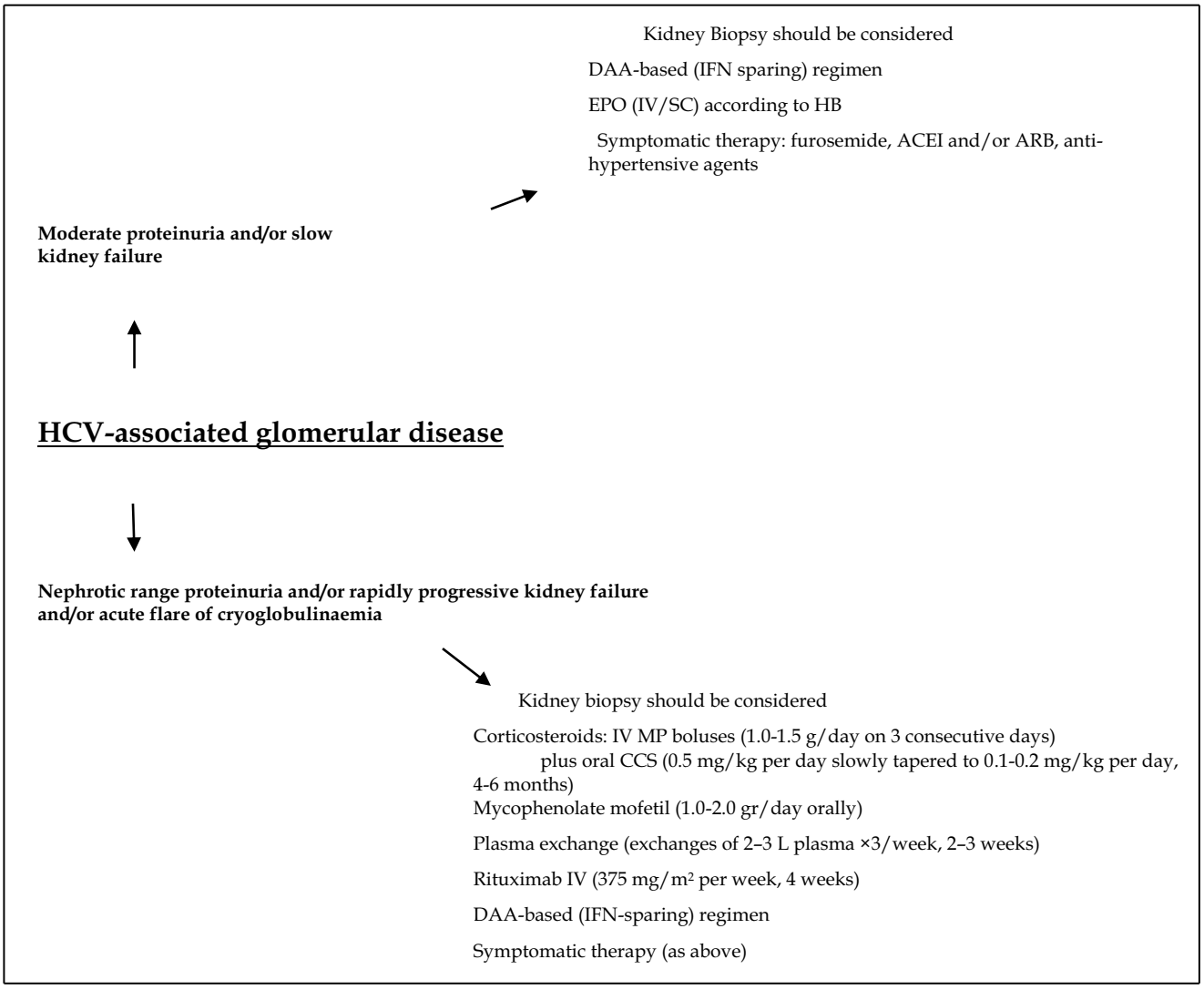

Fig. 3. Algorithm-based treatment of HCV-associated glomerular disease. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CCS: corticosteroid; DAAs: direct-acting antiviral agents; EPO: recombinant human erythropoietin; HB: haemoglobin; IV: intravenously; mcg: micrograms; MMF: mycophenolate mofetil; MP: methylprednisolone; peg-IFN: pegylated interferon; rIFN: recombinant interferon; SC: subcutaneously.

2 additional doses (1 and 2 months later)]. The mean follow-up was 72.47 ± 18.3 months and 31 patients (27 anti-HCV positive) with MC (type II, $n = 29$ patients; type III, $n = 2$ patients) were included. The most important comorbidities were as follows: severe skin ulcers ($n = 7$ patients), sensitive-motor neuropathy ($n = 26$), and diffuse membrano-proliferative glomerulonephritis ($n = 16$). In some patients ($n = 5$) immunosuppression therapy (three pulses of methylprednisolone, 500 mg each by IV route for three consecutive days) was also administered; no additional immunosuppressive agents or antiviral medications were given. The investigators observed complete remission of pre-treatment active manifestations in all patients with purpuric changes and non-healing vasculitic ulcers. Peripheral neuropathy improved in more than 80% of patients. Cryoglobulinemic nephropathy consistently improved during the observation period, starting from the 2nd months after RTX [serum creatinine, 2.1 ± 1.7 (baseline) to 1.6 ± 2.2 mg/dL (end of follow-up), $P < 0.031$; 24-h proteinuria, 2.3 ± 2.1 (baseline) to 0.8 ± 0.7 g (end of follow-up), $P < 0.01$)]. A consistent improvement of serological levels was also seen [cryocrit, 4.6 ± 1.1% (baseline) to 0.9 ± 1.1% (end of follow-up) ($P < 0.037$); C_4, 5.6 ± 7.4 (baseline) to 20.3 ± 8.0 mg/dL (end of follow-up) ($P < 0.021$); rheumatoid factor, 533 ± 1245 (baseline) to 198 ± 322 IU/ml (end of follow-up) ($P < 0.017$)]. No serious adverse events were found. The HCV RNA levels decreased, 5.7 ± 3.5 IU/ml × 10^5 (baseline) to 1.6 ± 1.6 IU/ml × 10^5 (end of follow-up) ($P < 0.04$).

After a mean of 31.1 (12–54) months, some ($n = 9$) patients showed signs of relapsing MC vasculitis and RTX was again administered. Six patients deceased due to cardiovascular disease, after a median follow-up of 55 months since RTX protocol.[36]

The safety of B cell depletion therapy for HCV-related glomerular disease remains controversial. According to a systematic review of the literature with meta-analysis of clinical studies, the treatment of mixed cryoglobulinemic syndrome with RTX has been associated with some infusion reactions but the frequency of discontinuation due to SAEs was not different between the two groups, RTX use (study group) *vs*. no RTX use (control group) (moderate certainty evidence).[37] One cycle of RTX for gastric lymphoma resulted in the occurrence of cholestatic hepatitis in a RT recipient with HCV. The patient had a long history of chronic hepatitis C, which up that point had been stable. An enormous increase of HCV RNA levels after B cell depletion therapy was found; the patient developed shortly bacterial pneumoniae and died due to respiratory failure.[38]

Treatment of HCV-related glomerular disease: non-selective immunosuppression

Plasma exchange is usually included in the guidelines for the management of HCV-related cryoglobulinemic vasculitis and glomerular disease.[1] The role of plasma exchange for HCV-related mixed cryoglobulinemic vasculitis is mostly limited to symptomatic hyperviscosity syndrome or life-threatening conditions such as pulmonary haemorrhage. Also, it has been suggested in the case of refractory conditions to conventional therapies. The aim of PEX is to obtain temporary clearance of circulating cryoglobulins from serum and to prevent their deposition in various organs and tissues including kidneys.[39]

The evidence in the medical literature concerning the adoption of mycophenolate mofetil for HCV-associated glomerular disease is extremely poor,[40] it has been administered by some clinicians instead of cyclophosphamide. Intravenous or oral corticosteroids are able to stop the inflammation at glomerular level; antiviral medications can support steroid use as these drugs inhibit HCV replication. The side effects related to cyclophosphamide use have hampered its use in these patients.[41]

Conclusions

The extensive and timely use of antiviral agents for the treatment of hepatitis C in the general population is limiting the development of cryoglobulinemic syndrome; thus, HCV-related cryoglobulinemic glomerulonephritis is becoming an uncommon disease. Successful antiviral therapy in patients with HCV-related glomerular disease is commonly associated with benefit, in terms of clinical/immunological response and kidney/patient survival. It appears that the introduction in the market of combinations of pangenotypic antiviral agents provided with fast activity and acceptable safety profile in patients with or without kidney impairment is limiting the adoption of immunosuppressive agents but this remains an area of avid research.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Funding

No sources of funding were used for the preparation of this manuscript.

Conflict of interest

The authors declare no conflict of interest.

Data availability

Not applicable.

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