CASE REPORT

Improvement of Proteinuria due to Combination Therapy with Daclatasvir and Asunaprevir in Hepatitis C Virus-associated Renal Disease without Cryoglobulinemia: A Case Report

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Abstract:
We herein report a unique case of hepatitis C virus (HCV)-associated renal disease without cryoglobulinemia that showed proteinuria, hypoproteinemia, ascites, and edema. Due to combination therapy with daclatasvir and asunaprevir, the patient achieved sustained virological response at week 24 of the therapy. Furthermore, the therapy caused marked amelioration of her proteinuria, ascites, edema, and hypoalbuminemia, and finally improved her estimated glomerular filtration rate. There were no adverse events, and the combination therapy was well-tolerated. We recommend that HCV eradication with antiviral therapy using direct-acting antiviral agents be attempted first for all renal disease with HCV infection, regardless of cryoglobulinemia, considering the existence of resistance-associated variants.

Key words: cryoglobulinemia, direct-acting antiviral agent, extrahepatic manifestation, hepatitis C virus, renal disease

Introduction

The most frequently reported kidney disease associated with hepatitis C virus (HCV) is HCV-associated glomerular disease (1), which is closely related to HCV-associated mixed cryoglobulinemia. HCV-associated glomerular disease includes a variety of kidney diseases, such as membranoproliferative glomerulonephritis (MPGN), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), and IgA nephropathy (2). Type I MPGN associated with type II mixed cryoglobulinemia is the most common HCV-associated glomerular disease (3). However, less commonly, there have been reports of HCV-associated renal disease without cryoglobulinemia, even in MPGN (1).

Direct-acting antiviral agent (DAA)-based therapy is the first-line therapy for patients with genotype 1 or 2 chronic hepatitis C in Japan, based on the most recent version (ver. 5.4) of the Japan Society of Hepatology (JSH) guidelines. Among DAA-based regimens, sofosbuvir is mainly metabolized in the kidney (4) and thus should be used cautiously for patients with chronic kidney disease (CKD) or in concomitant use with other renal excretory drugs. Specifically, a sofosbuvir-including regimen is contraindicated for patients with severe renal disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) or end-stage renal disease (ESRD) requiring hemodialysis.

Daclatasvir (DCV) and asunaprevir (ASV) are both mainly metabolized in the liver and can be used for patients with chronic renal dysfunction or dialysis (5-13). We herein report a case of HCV-associated renal disease without cryoglobulinemia in a patient who showed a sustained virological response at week 24 (SVR24) and marked amelioration of proteinuria and ascites by combination therapy with...
An 81-year-old woman infected with chronic hepatitis C developed ascites and edema in the lower limbs. She had been suffering from hypertension for 16 years. Her serum albumin level was 2.3 g/dL. Her hypoalbuminemia was thought to be due to a pathogenesis other than decompensated liver cirrhosis, based on the non-invasive scoring system of liver fibrosis and the laboratory data and imaging findings, as mentioned later. Two months after her initial presentation, her serum albumin level had decreased (1.7 g/dL), and urinary protein was positive on a urinary test strip, but cryoglobulinemia was not detected. She did not have diabetes mellitus, so diabetic nephropathy was interpreted as negative.

Given that her hypoalbuminemia was probably not due to decompensated liver cirrhosis and based on the unlikelihood of diabetic nephropathy and the positive urinary protein results, we considered that HCV-associated renal disease without cryoglobulinemia might have contributed to the proteinuria and hypoalbuminemia. However, we judged that pegylated-interferon therapy was not indicated for this patient because of her age (older patients are predicted to be intolerant to interferon [IFN]-based therapy) and her poor general condition, caused by abdominal distention, appetite loss, and edema. Therefore, we performed treatment for primary glomerular disease; a regimen of 20 mg/day prednisolone, an antiplatelet agent, diuretics, and a calcium channel antagonist was started, and the dose of the angiotensin II receptor blocker was increased, as poor control of hypertension can adversely affect the renal function.

However, the patient’s symptoms deteriorated further, and three months after starting the above-mentioned regimen, she was admitted to our hospital. We increased the dose of prednisolone (to 30 mg/day) and diuretics. We also started the administration of 100 mg/day cyclosporine and albumin. The determinate quantity of urinary protein was 3.4 g/day. Two weeks later, as improvement in her subjective symptoms was observed, although the serum albumin level remained unchanged, the dose of prednisolone was reduced to 20 mg/day; after another 2 weeks, it was reduced again to 15 mg/day, and she was discharged. The dose of prednisolone was ultimately reduced to 10 mg/day. Cyclosporine was used for nine weeks in total and discontinued because it was unlikely to be effective and we wanted to avoid infection. The patient was hospitalized another two times after this because of the deterioration of her subjective symptoms, so we increased the dose of diuretics and administered albumin each time. At the second of these later hospitalizations, edema in the lower limbs, ascites (Fig. 1a), and a deteriorated renal function were noted. We temporarily increased prednisolone to 15 mg/day from 10 mg/day, but improvement in the subjective symptoms was not obtained.

Considering the severity and treatment-intractability of this patient’s HCV-associated renal disease, we decided to try administering DAAs, which had just been approved for use in Japan at the time. Given the insufficient efficacy of prednisolone and the disadvantage of administering steroids for anti-HCV activity (14-16), we decreased the dose and then discontinued prednisolone before starting DAAs. The remaining concomitant drugs, such as diuretics, were not contraindicated for use in combination with DCV/ASV. Although the patient had Y93H, which is a resistance-associated variant, we started combination therapy with DCV/ASV, which was the only DAA covered by insurance and had just become available at the time, after we obtained full informed consent from the patient.

The patient’s characteristics are shown in Table. She had a rapid virologic response, and the transaminase level immediately normalized. Edema and ascites were improved and
Table. Laboratory Data.

|                           | Hematology                                                                 | Electrolytes and renal function |
|---------------------------|----------------------------------------------------------------------------|---------------------------------|
| WBC                       | 5,470 /μL                                                                 | BUN 19.2 mg/dL                  |
| Neutrophil                | 52.6 %                                                                    | Creatinine 0.7 mg/dL            |
| Lymphocyte                | 37.9 %                                                                    | Na 141 mEq/L                    |
| Monocyte                  | 5.8 %                                                                     | K 4.3 mEq/L                     |
| Eosinophil                | 1.8 %                                                                     | Cl 103 mEq/L                    |
| Basophil                  | 0.4 %                                                                     | tility mitochondrial M2 antibodies, ANA |<1.5 Occ |
| LUC                       | 1.50 %                                                                    | eGFR 59.8 mL/min/1.73 m²        |
| RBC                       | 451×10⁹ /μL                                                                | Markers of liver fibrosis       |
| Hemoglobin                | 14.5 g/dL                                                                 | APRI 1.16                       |
| Hematocrit                | 45 %                                                                      | FIB-4 index 3.66                |
| Platelet                  | 199×10⁹ /L                                                                | Viral markers                   |
| PT activity               | 92.7 %                                                                    | HBsAg (-)                      |
| Blood Chemistry           |                                                                           | HCV Ab (+)                      |
| TP                        | 6.7 g/dL                                                                  | Tumor markers                   |
| Albumin                   | 2.2 g/dL                                                                  | AFP 8.1 ng/mL                   |
| T-Bil                     | 0.7 mg/dL                                                                 | PIVKA-2 14 MAU/mL               |
| AST                       | 69 U/L                                                                    |                                |
| ALT                       | 59 U/L                                                                    |                                |
| LDH                       | 289 U/L                                                                   |                                |
| ALP                       | 260 U/L                                                                   |                                |
| γ-GTP                     | 46 U/L                                                                    |                                |
| ChE                       | 324 U/L                                                                   |                                |
| T-Chol                    | 205 mg/dL                                                                 |                                |
| Triglyceride              | 135 mg/dL                                                                 |                                |
| Glu                       | 113 mg/dL                                                                 |                                |
| HbA1c                     | 5.9 %                                                                     |                                |
| BTR                       | 2.78                                                                      |                                |

Two months before the start of the combination therapy with daclatasvir and asunaprevir

|                           | eGFR 39.3 mL/min/1.73 m² | HCV RNA 6.3 log IU/mL |
|---------------------------|--------------------------|-----------------------|
| CPK                       | 132 IU/L                 | Genotype 1b           |
| IgG                       | 622 mg/dL                | NS3 D168V (-)         |
| IgA                       | 447 mg/dL                | NS5A L31V (-)         |
| IgM                       | 77 mg/dL                 | NS5A Y93H slightly positive |
| C3                        | 100 mg/dL                |                       |
| C4                        | 32 mg/dL                 | Urine examination     |
| Cryoglobulin              | (-)                      | Color tone            |
| RF                        | 2.4 U/mL                 | Gravity 1.015         |
| ANA                       | <40                      | Protein 3.4 g/day     |
| AMA-M2                    | <1.5                     | Occult blood (+)      |
| PR3-ANCA                  | <1.0 U/mL                | RBC <1 HPF           |
| MPO-ANCA                  | <1.0 U/mL                | WBC 30 - 49 HPF       |
| CRP                       | 0.01 mg/dL               | Ketone (-)            |
| Sugar                     | (-)                      |                       |
| Bacteria                  | (2+)                     |                       |

γ-GTP: γ-glutamyltransferase, AFP: α-fetoprotein, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AMA-M2: antimitochondrial M2 antibodies, ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibody, APRI: aspartate aminotransferase to platelet ratio index, AST: aspartate aminotransferase, BTR: branched-chain amino acid-to-tyrosine ratio, BUN: blood urea nitrogen, ChE: cholinesterase, CPK: creatine phosphokinase, CRP: C-reactive protein, e-GFR: estimated glomerular filtration rate, FIB-4: fibrosis-4, HbA1c: hemoglobin A1c, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, HPF: high-power field, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, LDH: lactate dehydrogenase, LUC: large unstained cell, MPO: myeloperoxidase, PT: prothrombin, PIVKA-2: protein induced by vitamin K absence or antagonist-2, PR3: proteinase 3, RBC: red blood cell count, RF: rheumatoid factor, T-Bil: total bilirubin, T-Chol: total cholesterol, TP: total protein, UA: uric acid, WBC: white blood cell count.
The clinical course of the patient before and after combination therapy with daclatasvir and asunaprevir. The starting time of the combination therapy was described as 0 months, as shown on the horizontal axis of the graph. HCV RNA immediately became undetectable, and the serum ALT levels were normalized; eventually, a sustained virologic response at week 24 was achieved. The urinary protein significantly decreased to 1.7 g/day from 3.4 g/day at 13 months after the end of the treatment. Finally, the proteinuria disappeared, and the serum albumin increased to 3.9 g/dL at 28 months after the completion of the combination therapy. In addition, the serum creatinine and estimated glomerular filtration rate were improved at 28 months after the completion of the combination therapy. Alb: albumin, ALT: alanine aminotransferase, ARB: angiotensin II receptor blocker, ASV: asunaprevir, CCA: calcium channel antagonist, Cr: creatinine, DCV: daclatasvir, eGFR: estimated glomerular filtration rate, HCV: hepatitis C virus, PSL: prednisolone, SVR24: sustained virological response at week 24.

Discussion

HCV-associated glomerular disease is closely related to cryoglobulinemia (1, 17). However, HCV-associated glomerular disease without cryoglobulinemia has been reported. The severity of glomerular disease is not consistent with that of liver fibrosis (3, 18). Our case showed hypoalbuminemia and ascites. Although the FIB-4 index was 3.66, the aspartate aminotransferase-to-platelet ratio index was less than 2, and the total bilirubin, the number of platelets, and prothrombin activity were within normal ranges. CT did not show any findings of portal hypertension, such as splenomegaly. Furthermore, the branched-chain amino acid-to-tyrosine ratio (BTR) was 2.78. According to the receiver operating characteristic curve, the BTR indicated a...
cut-off point of 2.4 to discriminate between compensated cirrhosis and decompensated cirrhosis (19). The FIB-4 index was higher than 3.25 and suggested the existence of significant fibrosis (F3-F4) (20), but age, a component of the FIB-4 index, might have affected the grade of fibrosis, as our patient was elderly. Based on these laboratory data and fibrotic markers as well as imaging findings, our patient was deemed likely to have advanced chronic hepatitis or compensated liver cirrhosis but unlikely to have decompensated liver cirrhosis.

Her hypoprotenemia and ascites were thought to be mainly due to HCV-associated renal disease, as the disappearance of serum HCV RNA contributed to a decrease in the urinary protein. The proteinuria ultimately disappeared, but this took a long time to happen. Viral eradication does not always lead to disappearance of proteinuria. For example, in patients with HCV-associated glomerulopathies, including MPGN, MN, and mesangio-proliferative glomerulonephritis, treated by IFN alpha/ribavirin, the 24-h urinary protein values decreased significantly, from a mean of 4.8 g to 1.2 g, but the proteinuria was not always resolved in the subjects who responded to treatment (21). The effect of DAAs on the proteinuria of HCV-associated renal diseases lacks satisfactory evidence at this moment, so the period within which proteinuria disappears due to DAA therapy should be further evaluated with larger cohorts.

In HCV-associated glomerular disease, MPGN and MN are very frequent. MPGN is most often related to type II cryoglobulinemia and shows a significant reduction in the complement level. In contrast, MN largely shows a normal complement level and negativity of cryoglobulin (22). The pathogenesis of HCV-associated MN may be related to deposition of immune complexes containing HCV proteins in glomeruli, like hepatitis B virus (HBV) infection (23). The candidates of HCV-associated glomerular diseases in our case included MN, MPGN, IgA nephropathy (24), and FSGS (25, 26). Based on the normal complement level and negative findings for rheumatoid factor and cryoglobulin, MN was deemed to be more consistent with our case than MPGN. However, there have been some cases without cryoglobulin, as in the present case in MPGN (1, 4, 5). Notably, HCV-associated MPGN without cryoglobulin was ameliorated by combination therapy with DCV/simeprevir (27). Although the DAA regimen employed in that study was slightly different from ours, DAA therapy was proven to be effective for HCV-associated glomerular disease without cryoglobulin, and their findings support our data.

However, the qualitative test of cryoglobulin can provide a false negative due to inappropriate manipulation after the collection of blood. We only performed a qualitative test of cryoglobulin once before administering combination therapy with DCV/ASV in our patient. Although our institution strictly complies with instructions regarding the manipulation of the cryoglobulin test, testing of cryoglobulin should be performed multiple times to improve the accuracy of the diagnosis of the presence of cryoglobulin. However, we measured cryoglobulin at 28 months after the completion of the combination therapy with DCV/ASV, and the findings were still negative. In previous reports regarding cryoglobulin, the qualitative test was still positive at the end of treatment (10) or after 24 weeks of the combination therapy with DCV/ASV (11) or had decreased during the combination therapy (9). Thus, we believe that our case was likely a true-negative for cryoglobulinemia, although the combination therapy might have led to the resolution of cryoglobulinemia.

Our case was unlikely to have typical IgA nephropathy since erythrocytes were not detected in the urinalysis. However, occult blood was positive in the urinary test strip two months before the start of the combination therapy of DCV/ASV. Urinalyses were performed 4 and 5 months before and 14 months after the start of the combination therapy. The results of occult blood were negative or plus-minus on these analyses, and erythrocytes were never detected. Thus, the result of the occult blood test finding two months before the start of the combination therapy was considered to have been false-positive. Reasons for the discrepancy in the findings between the urinary test strip and urinary sediment include myoglobinuria, hemolysis, and bacteriuria, and so on. In our case, myoglobinuria or hemolysis were considered unlikely, as we observed no elevation in the total bilirubin, lactate dehydrogenase, creatine phosphokinase or no decrease in the hemoglobin level. The most plausible reason was bacteriuria, as an increase in the urinary white blood cell count and the presence of urinary bacteria were observed. However, there were no findings suggesting pyelonephritis, such as a fever or back pain, during the clinical course. Thus, the patient was most likely suffering from cystitis at the time when the discrepancy between the urinary test strip and urinary sediment was found, which affected the results of the urinary test strip.

In addition, IgA nephropathy and FSGS associated with HCV were thought to be rare compared with MPGN and MN. Considering the findings as a whole, MN is the most likely underlying renal disease in our case, although we cannot rule out other diseases. A pathological examination by a renal biopsy was desirable for a definitive diagnosis, but the patient’s poor general condition, including edema and ascites, prevented us from performing a renal biopsy.

In HCV-infected patients with renal disease, diabetes mellitus should be considered as the cause of renal disease, since HCV infection causes insulin resistance (28), and diabetic nephropathy is becoming the most frequent cause of ESRD in most countries (29). In our case, the blood glucose level, hemoglobin A1c, and urinary sugar were occasionally measured at her regular visits, and all of those values were within normal range. Therefore, we deemed her not to have diabetic nephropathy.

Several therapeutic approaches have been proposed for HCV-associated glomerular disease. The first is antiviral therapy to block the formation of immune complexes and the ensuing vasculitis due to HCV infection. The second is...
Although our case did not have cryoglobulinemia, antiviral therapy aimed at inflammatory cells that exist in vasculitic lesions (3). Because our case did not have cryoglobulinemia, we selected nonspecific immunosuppressive therapy, such as prednisolone and cyclosporine, along with symptomatic treatment, such as diuretics and albumin, except for antiviral drugs. However, prednisolone and cyclosporine were not very effective for our case because neither an increase in her serum albumin level nor a decrease in her urinary protein were evident during the administration period of these drugs. The improvement in the subjective symptoms was probably due to the albumin infusion and/or diuretics in our case. A late-developing effect of prednisolone was unlikely because the serum albumin level was relatively unchanged for approximately five months after prednisolone was discontinued. When therapy for HCV-associated renal disease was started in our case, DAA regimens without IFN had not yet been approved in Japan. IFN-based therapy was difficult to perform in our case because she had a poor general condition with renal disease. We therefore used combination therapy with DCV/ASV once this therapy became available. However, ombitasvir/paritaprevir/ritonavir (OBT/PTV/r), elbasvir/grazoprevir, and DCV/ASV/beclabuvir, which are now available for chronic hepatitis C patients with genotype 1 in Japan, are not contraindicated for severe chronic renal disease, which differs from sofosbuvir/ledipasvir. We are currently able to use these DAA regimens for HCV-associated renal disease instead of combination therapy with DCV/ASV.

As these IFN-free DAA-based therapies have a high efficiency and safety profile, and since some are suitable for use in elderly patients, CKD, ESRD patients (including dialysis patients), and IFN-intolerant patients, we feel that DAA-based therapy can be performed first for renal diseases in which HCV contributes to the pathogenesis, such as HCV-associated glomerular disease, regardless of the presence of cryoglobulinemia. In cases of diabetic nephropathy coexisting with HCV infection, HCV eradication may improve the condition of diabetes mellitus and thereby improve the prognosis of diabetic nephropathy. We therefore recommend that HCV eradication be first attempted for all renal disease with HCV infection, given the existence of resistance-associated variants. In fact, ver. 5.4 of the JSH guidelines recommend that antiviral therapy be performed aggressively for CKD and dialysis patients (Grade A), and the recommended antiviral therapy is an IFN-free DAA regimen selected according to the CKD stage.

Combination therapy with DCV/ASV has been reported to improve proteinuria, renal dysfunction, intractable edema, and vasculitis caused by cryoglobulinemia (9-11). However, the evidence level supporting the efficacy and safety of this combination therapy for patients with HCV-associated renal disease, especially those with severe renal dysfunction before the induction of dialysis, is insufficient, and the accumulation of more cases is desperately needed. Interestingly, although our case did not have cryoglobulinemia, antiviral therapy using combination therapy with DCV/ASV was effective, and we additionally observed a decrease in the urinary protein, an improvement in the serum albumin, and an amelioration of symptoms overall. We feel the present case is valuable because combination therapy with DCV/ASV helped improve the patient’s quality of life and her prognosis, even though she had cryoglobulin-negative HCV-associated renal disease. Our case supports the findings of previous reports (9, 10), which show that combination therapy with DCV/ASV improves the eGFR and serum creatinine levels in HCV-associated renal disease. However, DCV or ASV monotherapy is unlikely to affect the renal function (30). Although it has been reported that combination therapy with DCV/ASV significantly decreases the eGFR at 4 weeks, the eGFR remained within the normal limits (31). A recent study (32) showed that the rate of reduction in eGFR 40%-60% was only around 1% in HCV-infected patients with CKD treated with DCV/ASV combination therapy. Another recent study (33) observed no statistically significant differences in the eGFR between the pre- and post-treatment period in CKD patients receiving DCV/ASV combination therapy. These findings suggest that this regimen has a relatively safe profile concerning the renal function. However, more evidence should be accumulated regarding the effect on the renal function before any hard conclusions can be drawn.

Our study is limited by the lack of a renal biopsy due to the patient’s poor general condition and the fact that cryoglobulin was measured only once, before the combination therapy was started. Due to these limitations, the diagnosis of the underlying renal disease could not be confirmed.

In summary, we herein report a unique case of HCV-associated renal disease without cryoglobulinemia that showed proteinuria, hypoproteinemia, and ascites. Combination therapy with DCV/ASV induced SVR24 and caused marked amelioration of proteinuria, ascites, edema, and hypoalbuminemia, ultimately improving the eGFR. We recommend that HCV eradication with antiviral therapy using DAA families be attempted first for all renal disease with HCV infection, regardless of cryoglobulinemia, considering the existence of resistance-associated variants.

Author’s disclosure of potential Conflicts of Interest (COI).
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