

# Sofosbuvir and Daclatsvir in Treatment of Hepatitis C Virus-related Membranoproliferative Glomerulonephritis With Cryoglobulinemia in a Patient With Hepatitis C Genotype 4

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Direct antivirals showed dramatic response in hepatitis C virus (HCV) eradication, but their effect on extrahepatic manifestations is still unclear. A 49-year-old woman was referred to us suffering from lower limb edema and frothy urine. Renal biopsy was done and she was diagnosed with HCV-related membranoproliferative glomerulonephritis with cryoglobulinemia. Treatment with interferon plus ribavirin, steroid, and cyclophosphamide was tried but failed. After introduction of a sofosbuvir-based regimen to the treatment, sustained virologic response was achieved and nephrotic syndrome remission was induced successfully. We could conclude that HCV-related membranoproliferative glomerulonephritis with cryoglobulinemia could be treated successfully with immunosuppressive drugs plus sofosbuvir and dactalasvir.

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## INTRODUCTION

Mixed cryoglobulinemia is the most frequent extrahepatic manifestation of hepatitis C virus (HCV) infection. Patients with mixed cryoglobulinemia exhibit symptoms due to a systemic vasculitis of small- to medium-sized vessels (mixed cryoglobulinemia syndrome) in a percentage going from 5% to 30%.<sup>1</sup>

Membranoproliferative glomerulonephritis (MPGN) associated with type II mixed cryoglobulinemia remains the commonest form of kidney disease observed in direct relation to HCV.<sup>2</sup> There are currently no published reports documenting the efficacy of novel direct-acting antiviral regimens in patients with HCV-mixed cryoglobulinemia syndrome. Also, it is unknown if the patients will achieve sustained virologic response with typically prescribed treatment durations or will require a longer duration of treatment.<sup>3</sup>

## CASE REPORT

A 49-year-old female patient was referred to Mansoura Urology and Nephrology Center in 2013. Her main complaint was lower limb edema with frothy dark urine. Laboratory investigations revealed a serum creatinine of 0.8 mg/dL; serum albumin, 2.5 g/L; serum cholesterol, 308 mg/dL; alanine transferase, 18 IU/L, aspartate transferase, 20 IU/L; serum bilirubin, 0.5 mg/dL; hemoglobin, 13 g/dL; erythrocyte count,  $7.5 \times 10^9/L$ ; and platelet count,  $330 \times 10^9/L$ . Urine analysis revealed a protein level greater than 1000 by dipstick and 250 erythrocytes. A 24-hour protein collection in urine showed 8 g of protein. Virus serology results were a positive HCV antibody, HCV RNA polymerase chain reaction test, 850 000 IU/L. Rheumatoid factor was positive.

Clinical evaluation revealed elevated blood pressure, ascites, pitting lower limb edema, rash, tingling, and numbness of both lower limbs.

Normal findings were observed in abdominal ultrasonography and chest radiography.

Renal biopsy was performed and the patient was diagnosed with HCV-related MPGN with cryoglobulinemia. Biopsy details were 17 glomeruli per section. One was completely sclerotic. They all showed cellular proliferation and matrix expansion causing accentuation of lobulation in addition to capillary basement membrane thickening. Two showed wire loop lesions and leukocytic exudates. Minimal tubular atrophy and interstitial fibrosis was seen. Immunofluorescent microscopy revealed diffuse global granular immunoglobulin M and complement C3 deposits with marked intensity.

The patient was first treated with oral steroid, 40 mg, and oral cyclophosphamide, 100 mg, plus pegylated interferon, 180 mg/wk. Cyclophosphamide and interferon course was interrupted due to leukopenia and fever after 8 weeks. After recovery of erythrocyte count and fever, interferon course was resumed. A few days after resuming interferon, the patient developed fever and leukopenia again and interferon was suspended again. For 1 year, neither clinical nor laboratory remission occurred and HCV PCR was still high. The patient then received oral mycophenolate mofetil, 2 mg/d, instead of oral cyclophosphamide. After 3 months, there was partial improvement. Proteinuria decreased to 4.5 g/d. Serum albumin rose to 2.8 g/dL, lower limb edema disappeared, but rash was still present and the patient was still maintained on 2 antihypertensives.

Once creatinine clearance was higher than 30 mL/min, the patient started direct antiviral agents course including sofosbuvir, 400 mg, and daclatasvir, 60 mg, concomitant with 20 mg of prednisolone and 2 mg of mycophenolate mofetil. The course duration was 6 months. Hepatitis C virus RNA polymerase chain reaction test was negative after 1 month from the beginning of the course with normal liver function tests (Table).

Proteinuria significantly decreased to its minimum level during the disease course. Twenty-four-hour urinary protein became 1.2 g/d after 4 weeks from starting the direct-acting antivirals course. Also, serum albumin rose to 3.8 g/dL and cholesterol dropped to 180 mg/dL.

Clinically, lower limb edema and rash vanished. Blood pressure became controlled by 1 drug only. The improvement continued after direct-acting antivirals were discontinued, and 6-month sustained viral response was achieved. At the last follow-up, the patient was in complete remission and maintained on 5 mg of prednisolone and 1mg of mycophenolate mofetil. During the treatment course, there was no reported clinical or laboratory side effects.

## DISCUSSION

To the best of our knowledge, there are limited studies discussing this issue. Agarwal and colleagues reported the same results in 2016 with sofosbuvir and ribavirin.<sup>4</sup> Shimada and colleagues also showed successful treatment of HCV with dactalasvir and asunaprevir.<sup>5</sup>

In one study 48-week pegylated interferon- $\alpha$  and ribavirin was compared to sofosbuvir based regimen in treatment of HCV-related MPGN with cryoglobulinemia.<sup>6</sup> Sustained virologic response rate was higher with sofosbuvir with better clinical and laboratory findings. On the other hand, Gomis and coworkers observed a rise in serum creatinine in MPGN cases treated with sofosbuvir.<sup>7</sup> They claimed that sofosbuvir induced interstitial nephritis. Also, Cornella and coworkers suggested that longer treatment course (more than 24 weeks) was needed to treat HCV-related MPGN cases as most of their cases did not achieve complete remission.<sup>8</sup>

In conclusion, complete remission for nephrotic syndrome could be achieved after eradication of HCV using direct antiviral agents in MPGN cases associated with HCV concomitant with

Efficacy of Sofosbuvir and Dacalatasvir Regimen

Time from Treatment Initiation	Hepatitis C Virus RNA Polymerase Chain Reaction	24-Hour Urine Protein, g	Serum Creatinine, mg/dL	Serum Albumin, mg/dL	Complement C3
Baseline	853 465	3.5	0.8	2.8	Consumed
4 weeks	Negative	1.2	0.8	3.2	...
1 month	Negative	0.6	0.7	3.8	Normal
3 months	Negative	0.3	0.8	3.8	...
6 months	Negative	0.3	0.8	3.8	Normal

immunosuppressive drugs. Using direct-acting antivirals resulted in decrease immunosuppressive drugs to the lowest doses.

### CONFLICT OF INTEREST

None declared.

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