European Journal of Case Reports in Internal Medicine

Successful Treatment Using Simeprevir, Sofosbuvir and Rituximab of a Severe Form of Hepatitis C Virus-Related Mixed Cryoglobulinemia with Cardiac Involvement

Rafael Mahieu[1,2], Christian Lavigne[2], Geoffrey Urbanski[2], Isabelle Fouchard-Hubert[3], Alexandra Ducancelle[4], Françoise Lunel-Fabiani[4]

[1]Department of Infectious Diseases University Hospital, Angers, France,

[2]Department of Internal Medicine, University Hospital, Angers, France

[3]Department of Hepatology,University Hospital, Angers, France

[4]Department of Biology of Infectious Agents, University Hospital, Angers, France.

Doi: 10.12890/2015_000299 - European Journal of Case Reports in Internal Medicine - © EFIM 2015

Received: 29/09/2015
Accepted: 30/09/2015
Published: 11/11/2015

How to cite this article: Mahieu R, Lavigne C, Urbanski G, Fouchard-Hubert I, Ducancelle A, Lunel-Fabiani F. Successful treatment using simeprevir, sofosbuvir and rituximab of a severe form of hepatitis C virus-related mixed cryoglobulinemia with cardiac involvement. *EJCRIM* 2015;**2**:doi:10.12890/2015_000299.

Conflicts of Interests: The authors declare that there are no competing interests.

Acknowledgements: Rafael Mahieu drafted the initial manuscript, and approved the final manuscript as submitted. Christian Lavigne reviewed and revised the manuscript, and approved the final manuscript as submitted. Geoffrey Urbanski revised the manuscript. Isabelle Fouchard-Hubert reviewed and revised the manuscript, and approved the final manuscript as submitted. Alexandra Ducancelle reviewed and revised the manuscript, and approved the final manuscript as submitted. Françoise Lunel-Fabiani reviewed and revised the manuscript, and approved the final manuscript as submitted.

ABSTRACT

Numerous extrahepatic manifestations have been reported in hepatitis C virus (HCV) infection, particularly mixed cryoglobulinemia (MC). MC generally responds to clearance of HCV under pegylated-interferon plus ribavirin treatment. New direct-acting antiviral agents have been licensed for HCV under different combinations but have not been studied in severe forms of MC. Here, we present a case report describing a life-threatening form of MC with multivisceral involvement, which was successfully treated with concomitant rituximab, sofosbuvir and simeprevir. In light of the rapid clinical remission associated with sustained virological response and the excellent side-effect profile, this treatment should be considered as a first-line therapy in severe forms of MC.

LEARNING POINTS

- A life-threatening form of mixed cryoglobulinemia can occur in hepatitis C virus infection.
- Treatment with concomitant rituximab, sofosbuvir and simeprevir is one therapeutic option with an excellent side-effect profile.
- Despite clinical remission, cryoglobulinemia can remain detectable without clinical manifestations.

KEYWORDS

Mixed cryoglobulinemia; hepatitis C virus; sofosbuvir; simeprevir

European Journal of Case Reports in Internal Medicine

INTRODUCTION

Hepatitis C virus (HCV) infection is major cause of morbidity and mortality, affecting about 160 million people worldwide. Chronic infection is associated with an increased risk of cirrhosis, hepatocellular carcinoma and extrahepatic manifestations. Numerous papers have documented the link between mixed cryoglobulinemia (MC) and HCV infection, which affects 80–90% of patients with MC. Moreover, cryoglobulins (CGs) are found in 25–50% of patients with chronic HCV infection[1]. MC can be asymptomatic or have a wide range of clinical presentations. In particular, patients may develop symptomatic MC-related small vessel vasculitis with cardiac involvement. Mild forms are commonly cured with antiviral agents only (i.e. combination therapy with interferon and ribavirin), while life-threatening forms may require specific immunosuppressive therapy in addition to antiviral treatment. Recently, first generation direct-acting antiviral agents (DAAs) providing higher sustained virological response (SVR) were approved in Europe. Thus, a new panel of more active DAAs (i.e. sofosbuvir, simeprevir, daclatasvir, ledipasvir) and interferon-free regimens generally consisting of two or three DAAs with or without ribavirin, are now available. Also, a recent study found that long-term clearance of HCV led to persistent resolution or marked improvement of MC, suggesting the need for highly effective antiviral drugs. Here we describe a rare form of severe MC with cardiac insufficiency, glomerulonephritis and polyneuropathy in a patient with HCV genotype 1b infection effectively treated with rituximab and an interferon-free combination of simeprevir and sofosbuvir. To our knowledge, this is the first report of a successful triple therapy for this rare life-threatening complication of HCV-related MC.

CASE PRESENTATION

A 48-year-old woman was admitted to our hospital for dyspnoea and clinical signs of cardiac insufficiency. She had HCV genotype 1b (no previous treatment) with MC and suffered from psychiatric disorders. Her complaints were progressive shortness of breath over the preceding week, polyarthralgia, chronic pain and loss of feeling in her feet. Tests revealed haemolytic anaemia, acute renal failure, a type II MC and high viral load (*Table 1*). Clinical examination and transthoracic echocardiography (TTE) were consistent with severe cardiac insufficiency with a left ventricular ejection fraction of 30%. Coronarography and cardiac magnetic resonance imaging did not revealed any other abnormalities. A kidney biopsy showed membranoproliferative glomerulonephritis with subendothelial deposits. A diagnosis of severe MC with cardiac, renal, neurological, articular and cutaneous involvement was made.The patient was therefore prescribed rituximab 375 mg/m^2 weekly for 4 weeks together with a combination of simeprevir and sofosbuvir given for 12 weeks. The patient's weakness and arthralgia improved greatly within a week. No clinical complications were reported. Twelve weeks after the end of treatment, there was no detectable viral load and hepatic and kidney function had greatly improved (*Table 1*). TTE showed normalization of the left ventricular ejection fraction. After 1 year, the patient was still in clinical remission with SVR although the cryoglobulinemia was still detectable (0.2 g/l).

	At baseline	1 month after DAA+rituximab therapy	6-month follow-up
Heart failure (NYHA)	Class IV	Class II	Complete Resolution
Asthenia	Major weakness	Marked Improvement	Complete Resolution
Arthralgia	Intermittent	Stable	Stable
AST	84 IU/ml	43 IU/ml	20 IU/ml
ALT	70 IU/ml	23 IU/ml	10 IU/ml
Creatinine	169 µmol/l	110 µmol/l	75 µmol/l
Proteinuria	4 g/24 h	1.2 g/24 h	0.1 g/24 h
FM	0.1		0.4
FS	8.3 kPa		4.6 kPa
Viral Load[1]	7 log10 IU/ml	Undetectable	Undetectable
Cryoglobulinemia	0.19 g/l	0.19 g/l	0.2 g/l
C4	1 mg/dl	2 mg/dl	2 mg/dl
RF	Negative	Negative	Negative
IgM monoclonal	412 mg/dl	119 mg/dl	34 mg/dl

[1]Using the Abbott RealTime HCV assay.

AST: alanine aminotransferase; ALT: aspartate aminotransferase; FM: FibroMeter; FS: FibroScan; NYHA: New York Heart Association functional classification; RF: rheumatoid factor.

Table 1 Patient data at baseline and during follow-up.

DOI: 10.12890/2015_000299

European Journal of Case Reports in Internal Medicine

DISCUSSION

HCV-related MC may result in acute or progressive life-threatening organ damage with a mortality rate of 20–80%[2]. Much therapeutic progress has been made since the initial treatment of MC with interferon alpha in 1987 and the discovery that HCV was its main aetiological agent. Pegylated interferon-alpha (PEG-IFNα) combined with ribavirin improves overall MC clinical response and SVR in up to 60% of patients. Rituximab has been successfully used in MC. Several trials have shown that rituximab has better efficacy than conventional treatments[3] and that it seems to be safe in HCV patients, in contrast to patients with hepatitis B virus. Controlled clinical trials have also demonstrated that PEG-IFN/ribavirin plus rituximab compared to PEG-IFN/ribavirin alone resulted in better clinical remission and CG clearance; those Authors proposed the use of rituximab in patients with severe vasculitis, with or without plasmapheresis, before initiation of antiviral therapy. First-generation DAAs (boceprevir or telaprevir) in combination with PEG-IFNα and ribavirin have been shown to provide higher (up to 75%) SVR in HCV genotype 1. They have also been demonstrated to be very effective in MC[4] but with high rates of side effects. Since 2014, new DAAs with improved side effect profiles and SVR levels (>90%) have been approved. An interferon-free combination of daily sofosbuvir and simeprevir for 12 weeks was recently studied and validated by international recommendations[5] in patients with genotype 1 HCV.

In the absence of other explanations, we attributed the cardiac insufficiency in our patient to MC, despite its rarity in this setting (less than 5% of MC[2]). Cardiac involvement is associated with a poor survival rate[2]. Thus, in light of the association between glomerulonephritis and neuropathy, it was decided to institute a highly effective treatment targeting both autoimmunity and viral triggers. Plasmapheresis was not performed because of patient refusal. The psychiatric disorder contraindicated interferon, while ribavirin was ruled out because of risks associated with the haemolytic anaemia. Finally, rituximab was started after initial management of acute decompensated heart failure, together with daily sofosbuvir (400 mg) and simeprevir (150 mg) for 12 weeks. This combination has not been previously studied in severe forms of MC, as rituximab is generally started before antiviral treatment. Despite the life-threatening condition of our patient with severe cardiac and kidney involvement, this triple therapy of sofosbuvir, simeprevir and rituximab resulted in a spectacular, rapid and complete clinical recovery with normalization of cardiac function and virological response, without any side effects. This first description of an interferon-free combination of new DAAs with rituximab is particularly encouraging and could be proposed as a first-line treatment for severe HC-related MC.

REFERENCES

1. Lunel F, Musset L, Cacoub P, Frangeul L, Cresta P, Perrin M, et al. Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. *Gastroenterology* 1994;**106**:1291–1300.
2. Terrier B, Karras A, Cluzel P, Collet J-P, Sène D, Saadoun D, et al. Presentation and prognosis of cardiac involvement in hepatitis C virus-related vasculitis. *Am J Cardiol* 2013;**111**:265–272.
3. De Vita S, Quartuccio L, Isola M, Mazzaro C, Scaini P, Lenzi M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012;**64**:843–853.
4. Saadoun D, Resche Rigon M, Pol S, Thibault V, Blanc F, Pialoux G, et al. PegIFNα/ribavirin/protease inhibitor combination in severe hepatitis C virus-associated mixed cryoglobulinemia vasculitis. *J Hepatol 2015*;**62**:24–30.
5. American Association for the Study of Liver Diseases. Recommendations for testing, managing, and treating hepatitis C. 2015. www.hcvguidelines.org/full-report-view